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ENDOTHELIOMAS

WITH SPECIAL REFERENCE TO THOSE GROWING IN A COMPACT FORM

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There can be but few forms of new growth about whose nature there is so much divergence of opinion as the endotheliomas. Hemangiomas form a fairly well defined type of growth, but even such allied conditions as the lymphangiomas are far from clearly characterized. These difficulties account for the fact that some pathologists regard endotheliomas as being quite common tumors, while others make such a diagnosis only in rare instances and, even then, with a good deal of hesitation.

The diagnosis of the clearly recognizable forms of endothelioma depends mainly on the arrangement of the constituent cells rather than on the structure of the individual component elements; this is unavoidable in the absence of any clear idea as to the morphology of endothelial cells in general. Lazarus-Barlow [1] published a most excellent account of the appearances of normal endothelial cells stained by ordinary histologic methods. He speaks of them as being regularly arranged with "a large round or oval nucleus and with a large amount of protoplasm to the cell. As a rule, the chromatin is collected round the periphery of the nucleus and also in the center, while strands of chromatin extend between the two. Hence, in section, the nucleus is remarkable by its clearness and its appearance of vacuolation." Mallory [2] pointed out another feature which he regarded as being characteristic of these cells, viz., the absence of formation of fibrils in contradistinction to the habit of neuroglial cells. My own experience certainly confirms all these statements in those specimens examined only by ordinary staining methods.

It is obvious that these older accounts must be amplified by reference to more recent conceptions as to the nature of the reticulo-endothelial tissue; this has been so admirably summarized by Aschoff [3] that no reference to the literature is desirable here.

1. Lazarus-Barlow, W. S.: Arch .Middlesex Hosp. **7**:79, 1906.
2. Mallory, F. B.: Boston M. & S. J. **159**:137, 1909.
3. Aschoff, L.: Ergebn. d. Inn. Med. u. Kinderheilk. **16**:1, 1924.

The first description of reticulum as a special form of supporting tissue is due to Mall,[4] who described the framework of many organs as being composed neither of white fibrous nor of yellow elastic tissue, but of a third kind of supporting substance. He stated that this new tissue was composed of fine interlacing fibrils, and named it "reticulum." In a later paper,[5] he described the mode of formation of these fibrils from the mesenchymal syncytium, but pointed out one exception to this method of development, namely, in the liver, in which the fibrils were found to arise from the Kupffer cells. This seems to have been the first account of the structure of a "reticulo-endothelium" in a morphologic sense. Ranvier[6] was not able to observe this relationship between cells and fibrils and came to the conclusion that the former were simply wrapped around the latter.

Although Mall had shown that one particular variety of "endothelial" cell was capable of producing reticular fibrils, it was not until the work of Corner[7] in 1920 that the widespread occurrence of fibrils developed in this way was clearly recorded. Downey[8] carried out a similar investigation with special reference to the relationships of reticulum and endothelium in mammalian lymph nodes. He demonstrated that the lining of the sinuses in these structures was essentially of a reticular character and that the fibrils were directly derived from the cytoplasm of those lining cells which are commonly regarded as being endothelial. He objects to the idea that a cell capable of producing fibrils should be termed endothelial, but, in fact, although not in so many words, contributes greatly to a better understanding of the morphology of reticulo-endothelium, particularly, as he makes it clear that these cells of which he writes are actively phagocytic.

It must be clear that such histologic data require consideration in the study of endothelial tumors, because the question arises as to whether the cells of such neoplasms can also produce fibrils, and also whether both solid and vascular endothelial growths show this property.

There are, of course, other difficulties, of which the satisfactory classification of these growths is not the least. Ewing[9] has done much to clarify the nomenclature of the subject; his arrangement is as follows:

1. Interfascicular: The cells grow in narrow layers between strands of connective tissue. Swelling and hyaline change in the stroma entitles the growth to the name cylindroma.

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4. Mall, F. P.: Johns Hopkins Hosp. Rep. **1**, 1896.
5. Piney, A.: Brit. J. Surg., in press.
6. Ranvier, L.: Arch. d'anat. micr. **1**:137, 1897.
7. Corner, G. W.: Contrib. to Embryol. Carnegie Inst. Washington **9**:85, 1920.
8. Downey, H.: Haematol. **3**:431, 1922.
9. Ewing, J.: Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1922.

2. Alveolar: The cells grow in small or large groups as in adenoma. When seen in longitudinal sections, they show a tubular arrangement.

3. Plexiform: The cells grow in convoluted columns often surrounding vascular paths.

4. Perivascular: The cells surround definite vascular channels.

5. Diffuse: The cells grow diffusely or without definite arrangement.

6. Miscellaneous: These represent nothing more than the result of various progressive and regressive changes in the stroma.

This classification is, I believe, a most excellent one if purely general arrangement be a sufficient guide to nomenclature, but any arrangement not based on the details of cell structure can be only a temporary one, and tumors derived from reticulo-endothelium also need to be included in the scheme in order to make it complete.

Kettle and Ross [10] attempted to introduce more definite criteria by which to recognize the neoplastic endothelial cell. They chose the hemangiomas for their investigation as representing a group of tumors of whose endothelial nature no doubt could be entertained. They laid much stress on the frequency with which intracellular vacuolation was seen in the tumor cells, and interpret this as evidence of their vasoformative potentialities. "If we recognize that the lumen of endotheliomata are produced in a definite way as an attempt at functional activity on the part of the neoplastic cell, it should enable us to distinguish them from such formations in the carcinomata either from necrosis or from incomplete development into glandular tissue." It must, of course, be borne in mind that not all parts of every hemangioma show the development of obviously vascular channels; some areas may be composed of compact masses of cells. Fraser [11] showed that such compact areas and even completely solid endothelial tumors might arise by proliferation of the cells of a neoplasm of ordinary angiomatous type, i. e., it is not always possible to detect signs of vasoformative activity in all parts of such a growth; nevertheless, he is of the opinion that all hemangiomas are of capillary origin. It is equally certain that compact endothelial tumors are not necessarily more malignant than those of obviously vascular type, and there is no reason for presuming that their component cells are always more "anaplastic."

Compact endothelial tumors derived from lymphatic endothelium are also known, but there is no information as to the functional activities of the component cells of either compact hemendotheliomas or lymph-endotheliomas. It would seem possible that the cells of compact endothelial tumors exercise a function of fibril formation rather than of

10. Kettle, E. H., and Ross, J. M.: Lancet **1**:1012, 1921.

11. Fraser, J.: Brit. J. Surg. **7**:335, 1920.

vasoformation, but the only observations on this subject are those of Foot,[12] which deserve detailed description.

The case which Foot records under the name of "malignant endothelioma" occurred in a woman, aged 68, who, in addition to an apparent osteomyelitis of the left wrist, presented a swelling in the right groin. At necropsy, metastases were found in the regional lymphatic glands and also in the lungs. Foot was uncertain of the site of origin of the primary growth because the left wrist was not examined at necropsy. The histologic features of the inguinal tumor are described in detail, and he comments on the large number of mitotic figures and of giant cells seen in all the sections. The most striking feature of the neoplastic cells seems to have been their tendency to anastomose with one another by means of more or less raylike processes. He writes: "It appears to me as though some of the cells form reticulum, while others that lie free of it do not participate in its formation." He favors the view that this tumor is an example of a growth arising in reticulo-endothelial tissue, and writes, "The reason for harping on reticulo-endothelium in this case is obvious; we must explain the formation of reticular fibrils by the tumor cells. The morphologic differences between vascular and reticulo-endothelium may, after all, be merely an evidence of a difference in the physiology of the same cell in varying surroundings." In this connection, he mentions a case observed by R. S. Austin in which an angio-endothelioma of the parotid was associated with endotheliosarcomas in the skin, breast, heart, etc. His description and comments here are important: "Sometimes the cells form vascular structures, sometimes alveolar, sometimes discrete. They also exhibit phagocytic propensities. The striking feature of this tumor is that the lymph node metastases have no tendency to grow in a vascular arrangement, but resemble our tumor so closely that sections of tissue from the two cases would be indistinguishable, were it not for the far greater number of mitoses in ours. Here, then, we have corroboration of the endothelial origin of our tumor and strong indication that it may be derived from vascular rather than reticulo-endothelium."

The illustrations of Foot's paper seem to show the following essential features in the histologic structure of the growth:

(*a*) Reticulum fibrils in direct connection with the cells.

(*b*) Formation of multinucleated giant cells.

(*c*) Attachment of the tumor cells to structures, which might well be walls of lymph sinuses.

Foot appears to have shown clearly that vascular and reticulo-endothelium are not rigidly different tissues, but are interchangeable in

12. Foot, N. C.: J. M. Res. **44**:417, 1924.

varying environmental conditions. This thesis, which is so essentially new, is one of the subjects which I shall discuss.

Foot's case seems to be the only one of this type on record, but Meyerding [13] figures a "medullary sarcoma of tibia containing giant cells," which seems to bear a close resemblance to Foot's tumor. Ewing writes of the large cell type of lympho sarcoma as being a "reticulum cell" sarcoma, and his picture (fig. 152) seems very like those published by Foot, although the reticular fibrils are, of course, not shown. It is highly probable that Ewing's photograph would, by many, be interpreted as representing a malignant endothelioma, and, in fact, Foot claims that this is a condition closely allied to lymphosarcoma. Simonds [14] has also supported the essential identity of lymphosarcoma and leukemia as seen in mice, so that it is justifiable here to discuss briefly whether any other conditions are known to affect this reticulo-endothelial tissue in such a manner as to occasion a tumor-like hyperplasia.

The only disease, other than those already mentioned, in which I have been able to detect participation of the reticulo-endothelial tissue in the pathologic process is Hodgkin's disease, and it is convenient to describe the observations briefly before passing on to the consideration of the real subject of this paper. I [5] have elsewhere suggested that Hodgkin's disease is to be regarded as being essentially a proliferation of reticulo-endothelium and its derivatives, and this seems to be a view which has been held in rather less detail by other writers, and has been noted by many who have not appreciated the significance of the appearances. MacCallum, for example, states that lymphadenoma is "not an example of the hyperplasia of either myeloid or lymphatic tissue." Reed,[15] who wrote her classical paper before any conception of a reticulo-endothelial system had been formulated, stated: "These so-called endothelial cells (in Hodgkin's disease) we do not believe are identical with the endothelium of the blood vessels and large afferent and efferent lymphatic sinuses. . . ." "They are, in reality, only a species of flattened out connective-tissue cells." "In proliferating, they form epithelioid cells, having large vesicular nuclei, with a heavy chromatin network and one or more nucleoli." She also derived the characteristic giant cells of this malady from these cells. This disease is of importance in the present study only because some cases show sarcomatous properties, and Ewing writes: "In a recent study of thymus tumors I have collected evidence suggesting that many of the cases of Hodgkin's disease exhibiting sarcomatous qualities originate in the thymus, and that the peculiar characters of the infiltrating cells are referable to their origin from the

13. Meyerding, H. W.: Surg. Gynec. & Obst. **24**:321, 1922.

14. Simonds, J. P.: J. Cancer Res. **9**:329, 1925.

15. Reed, D. M.: Johns Hopkins Hosp. Rep. **10**:133, 1902.

epithelial reticulum of the thymus." It is probable that very few will be inclined to agree with the idea of an "epithelial" reticulum in the thymus, but, nevertheless, Ewing has made clear that "Hodgkin's sarcoma" is of the nature of a "reticulum cell" sarcoma, that is, is a malignant reticulo-endothelioma. It would seem to follow from this that the more usual form of Hodgkin's disease must also be an affection of this tissue.

The view that lymphosarcoma and endothelioma are related pathologic conditions seems to be a widespread one, and is emphasized by Foot. It is so well recognized that lymphocytes do not, as a rule, show much sign of phagocytic activity, that one may be surprised at the frequency with which the cells of lymphosarcomas show this property, and it is tempting to imagine that here again the reticulo-endothelium plays a part in the formation of these growths, that is, that the relationship claimed by Foot is rather between the reticulo-endotheliomas and the lymphosarcomas than between the whole group of endotheliomas and the lymphosarcomas. It is hoped to demonstrate in the latter part of this paper that all "endotheliomas" possess a reticular component although in varying amount.

It is necessary to refer briefly to that group of tumors often termed peritheliomas. It is not even certain that such a tissue as perithelium exists in a form deserving a special name, although Zeit [16] states that "the perithelium is the outer lining of the adventitia of blood vessels, outside of which is the perivascular lymph space." Bayon [17] devoted much attention to the tumors reputed to arise from this tissue, and came to the conclusion that all growths presenting a radial disposition of cells around blood vessels the endothelium of which was intact might be termed peritheliomas, even if it could not be conclusively shown that they originated from the perithelium. It is clear that such an arrangement as that postulated by Bayon might arise by involvement of perivascular lymphatics or even as a result of paravascular degeneration of tumor tissue. In the present paper, the term "peritheliomatous arrangement," will be used simply as a topographic description with no genetic significance, a course of action properly suggested by Roussy.[18]

The first two cases to be described here demonstrate widespread formation of fibrils by "endothelial" cells in a manner similar to that recorded by Foot.

REPORT OF CASES

CASE 1.—The first case was that of a woman, aged 75, who complained of the presence of a lump in the right groin and of abdominal distention. The

16. Zeit, F. R.: J. A. M. A. **46**:567, 1906.

17. Bayon, P. G. E.: Brit. M. J. **2**:195, 1907.

18. Roussy, G.: Atti del 1 Congr. dei Patol, Turin, **20**, 1911.

duration of her illness had been only about one month. The mass in the groin was bluish black, and a clinical diagnosis of melanotic sarcoma was tentatively made.

At necropsy, the lump in the right inguinal region was found to be discolored simply as a result of bleeding into its substance, and a number of other masses of similar tissue were found on its deep aspect.

The abdomen contained some excess of fluid, and innumerable minute tumor-like masses had caused enormous thickening and shortening of the omentum. Many deposits were also found in the mesentery, particularly along its intestinal attachment.

Metastases were found in the right pleura, in the liver and on the under-surface of the diaphragm.

The histologic appearance of the tumors was striking: there seemed to be a heterogeneous mixture of cell types presenting a variety of arrangement in different parts. Most of the present description is based on the study of the growths in the inguinal region.

In many places, there was a "peritheliomatous" arrangement of the cells around thin-walled blood vessels with intact endothelial lining. In most places the masses of cells were divided up by branching septums, and many cells seemed to have definite attachment to these strands. Frequently the cells were seen to radiate from such a septum instead of from a blood vessel. Small areas of necrosis were numerous and seemed to bear no notable relationship to vessels. The surface of the largest mass in the groin was covered with a fibrous capsule, and under this, the arrangement of the tumor tissue seemed to present many of the appearances of a lymphatic gland, as the fibrous capsule was separated from the growth by a space resembling the peripheral sinus of a lymph node. The reticular septums themselves appeared to arise from the walls of thin-walled channels of indeterminate nature.

Examination of the sections with high magnifications showed that the great majority of the cells conformed to one type, although a considerable number of giant cells were mixed with the predominant small cells. The nuclei showed an edge of chromatin and a variable number of chromatic knots nearer the center, but were really rather poorly supplied with this substance. The majority of the cells, even the smallest ones, had abundant protoplasm, which ran out into raylike processes and so made connection with adjacent cells. The characters of the nuclei and cytoplasm of the giant cells so closely resembled those of the smaller cells that they could be regarded only as neoplastic variants of the more ordinary type of cell. The intimate connection of cells and fibrils was even more easily appreciated in parts of the growth where both these structures were cut longitudinally.

The mode of origin of the fibrils from the cells was by no means easy to determine. Sections were impregnated with gold and silver (Foot's method), but the histologic picture was, even then, very obscure. The nature of the finely granular appearance of the cytoplasm (fig. 1) was very difficult to interpret. I came to the conclusion that it represented innumerable minute intracellular fibrils impregnated with silver, and, in places emerged as a more solid fibril from the protoplasm of the cell. The appearances were so difficult to determine and interpret that I asked Dr. W. J. Purdy of the National Institute for Medical Research to examine sections. He prepared the drawings from which figures 2 and 3 were prepared, and I am extremely grateful to him for the endless trouble he took in the matter. Figure 2 shows the appearances of a small group

of cells, while figure 3 shows a more schematic appearance intended to represent the actual structure of the cells as we interpret it. It is notable that the appearances are very much like those described by Corner in normal endothelial cells.

The various metastases showed a structure very much like that seen in the primary growth, and there was good evidence that spread had occurred by way of the lymphatics. The channels on the surface of the mesentery, particularly near its attachment to the intestine, were filled with tumor cells, and, in the substance of the mesentery, it was possible to find channels almost completely plugged with the cells (fig. 4). The structure of these invaded channels throws an interesting light on the mode of dissemination of this tumor. The lumen of the channel shown in figure 4 is practically filled with tumor cells resembling those seen in the primary growth, but the most striking feature is the almost

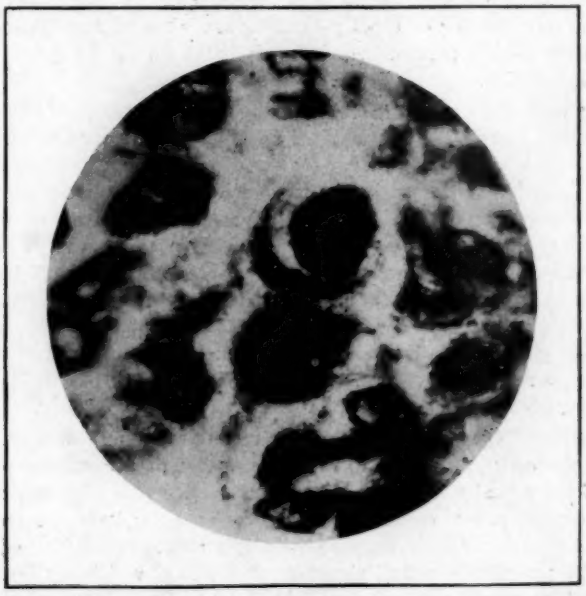

Fig. 1.—"Endothelioma" from inguinal region; × 1,000. The common crescentic type of cells is seen as is also the very finely granular character of the silver-impregnated cytoplasm.

complete absence of the normal endothelial lining. The greater number of the lining cells seem to have been replaced by characteristic tumor cells lying in direct contact with the outer coats of the channel. These appearances in the lymphatics are difficult to interpret as it is not possible to determine with certainty whether there is direct transference of tumor cells from one place to another along their lumen or whether the spread of the growth depends on "infection" of the normal lining cells by the neoplastic process such as Best [19] described as occurring at the edge of some endotheliomas. Neelsen [20] and also Schulz [21] contend that metastases may arise from such growths purely as a result

19. Best: Beitr. z. path. Anat. u. f. allg. Pathol. **23**:253, 1898.

20. Neelsen: Deutsch. Arch. f. klin. Med. **31**:375, 1882.

21. Schulz: Arch. f. Heilk. **17**:1, 1876.

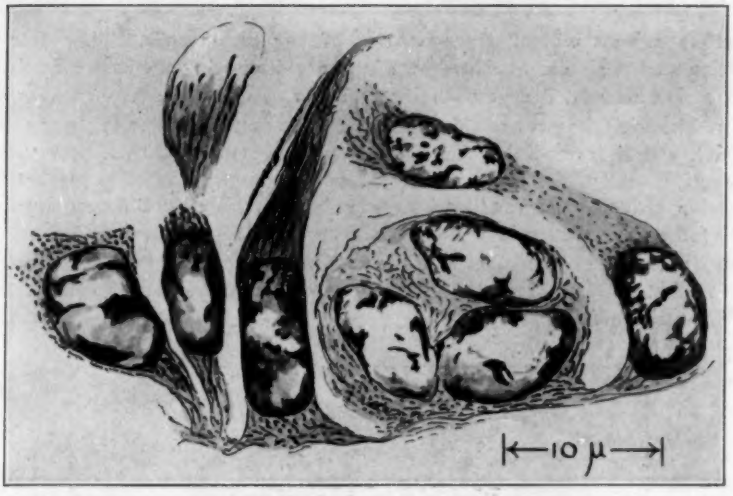

Fig. 2.—Drawing of histologic appearances in "endothelioma from inguinal region (by Dr. W. J. Purdy). Exact histologic appearances of the intracellular fibrils and of their mode of emergence from the cell. The drawing has been made with photographic accuracy, but with more than photographic clarity. The fine fibrils here seen correspond with the indistinct granularity of the cytoplasm seen in figure 1.

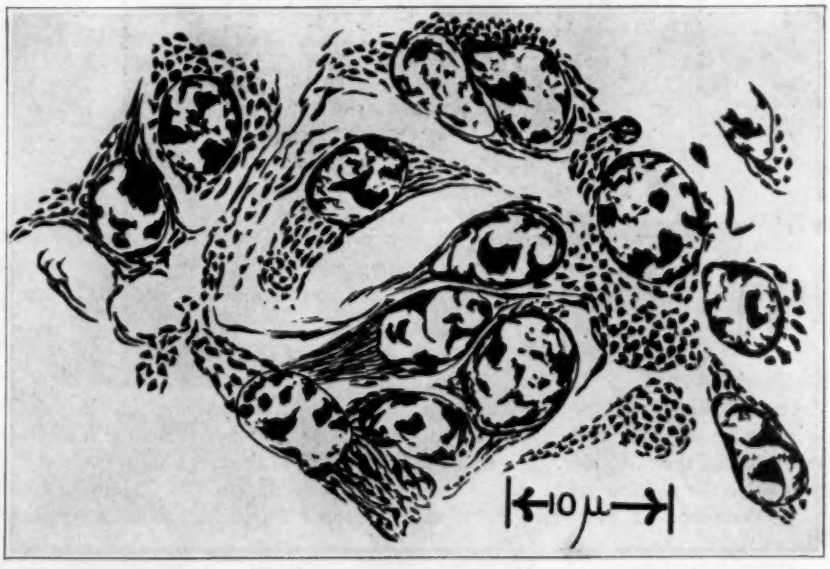

Fig. 3.—Drawing to illustrate the true structure of the tumor cells (by Dr. W. J. Purdy). Interpretation of the structures shown in figure 2 as determined by careful focusing of the section with subsequent preparation of a sort of composite picture of the different levels. If this interpretation is accepted as correct, it is obvious that intracellular fibrils emerge from the tumor cells to form a reticulum in the intercellular spaces.

of such a process without transportation of any tumor cells. They describe a condition almost similar to that shown in figure 4 as being the basis of this mode of extension, namely, the lymphangitis prolifera of Schweniger.[22]

The histologic features of this case seem to be almost similar to those recorded by Foot, and it seems fairly certain that we have to do with a tumor derived from reticulo-endothelium, particularly as no evidence was found to support Foot's contention that vascular and reticulo-endothelium are only different manifestations of the same tissues in varying conditions.

One other case of malignant reticulo-endothelioma is worthy of record as showing that such neoplasms are not excessively rare, and also because a unique case is available for discussion.

Fig. 4.—Lymphatic in substance of mesentery; × 150. The greater part of the lumen of the channel is filled with tumor cells, and the normal endothelial lining is almost completely replaced by similar elements.

Case 2.—The case was that of a man, aged 47, who had noticed a swelling on the middle finger of his right hand for about five years. During the six months prior to coming under observation, he had observed the development of a lump in the axilla of the same side. On examination, the swelling on the finger was found to involve the metacarpal bone as well as the phalanx; the axillary lump appeared to be composed of enlarged glands, and another small subcutaneous nodule was discovered on the forearm.

The affected finger with its metacarpal bone was removed. The tumor seemed to arise from the tendon sheath without involvement of the tendon itself. The histologic characters of the growth were strikingly variable in different parts of the mass. Parts of the growth showed characters closely resembling those seen

22. Schweniger: Ann. d. allg. Krankenhaus München, 1878.

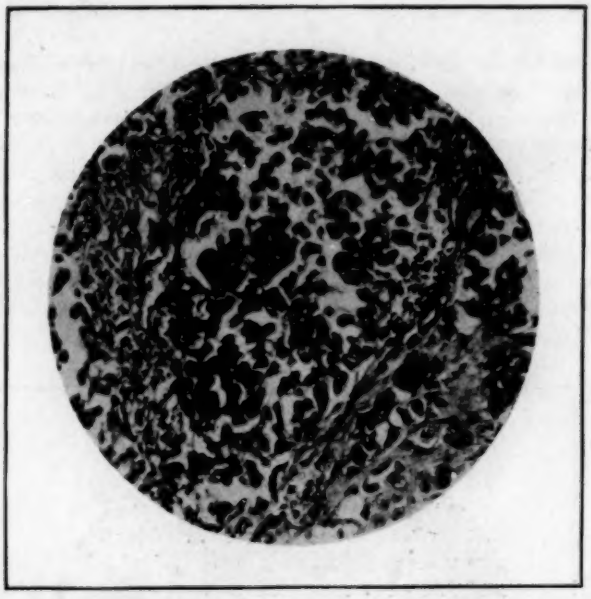

Fig. 5.—Malignant "endothelioma" from tendon sheath; × 150. The greater part of the growth showed these appearances, namely, masses of cells lying in spaces bounded by irregular septums to which the cells bore close relationship.

Fig. 6.—Malignant "endothelioma" from tendon sheath; × 600. The origin of reticular fibrils from the protoplasm of the "endothelial" cells can be seen, although the structure is best appreciated by comparison of the structure with that shown in figures 2 and 3.

in the first case; there were fine septums enclosing masses of cells, some of which lay in immediate contact with the septal fibrils (fig. 5). It was possible to observe the origin of fibrils from cells just as in the previous case (fig. 6). In one place, the tumor mass lay near the skin, and here there was a distinct alteration in type; the amount of stroma was much increased and the cells compressed and degenerate (fig. 7). The appearances were identical with those of a "cylindroma," which cannot, therefore, be regarded as a special type of tumor.

The histologic features seemed to suggest the reticulo-endothelial character of the neoplasm so very clearly that it was thought of importance to inject India ink in an attempt to confirm this view. The patient had no objection to so experimental a method of treatment, and therefore 8 cc. of India ink in saline were

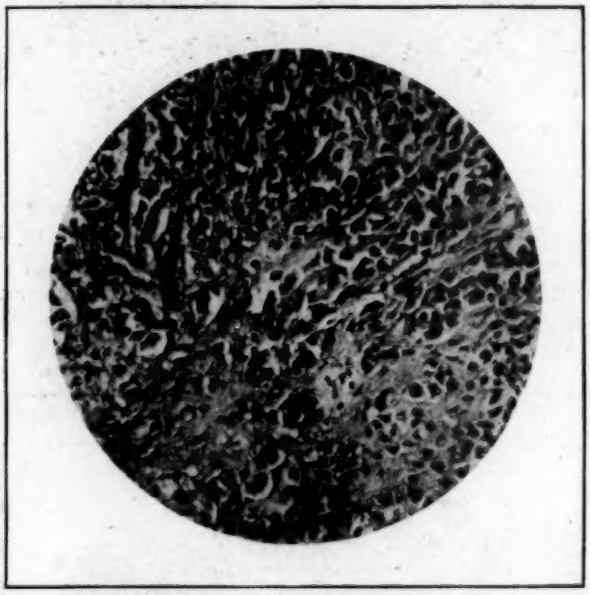

Fig. 7.—Malignant "endothelioma" from tendon sheath; × 150. This portion of the growth, which shows a "cylindromatous" structure, came from near the skin.

injected into a vein in the forearm two days before the axillary glands were to be removed. It was not particularly disappointing that no traces of the ink could be found in the metastases, because the amount was presumably far too small to be discoverable anywhere in the body after dilution in the circulation.

The axillary glands showed macroscopic appearances almost similar to those of the primary growth, but the small subcutaneous mass in the forearm was hard and white like that part of the primary growth which lay immediately under the skin.

The histologic characters of the metastases differed very little from those of the primary growth, and the small nodule was "cylindromatous."

There is, as is well known, a peculiar giant cell growth of tendon sheaths, which is variously interpreted as being a mass of granulation tissue, a xanthoma or even a sarcoma of low maligancy. In any case, there is no record of such a

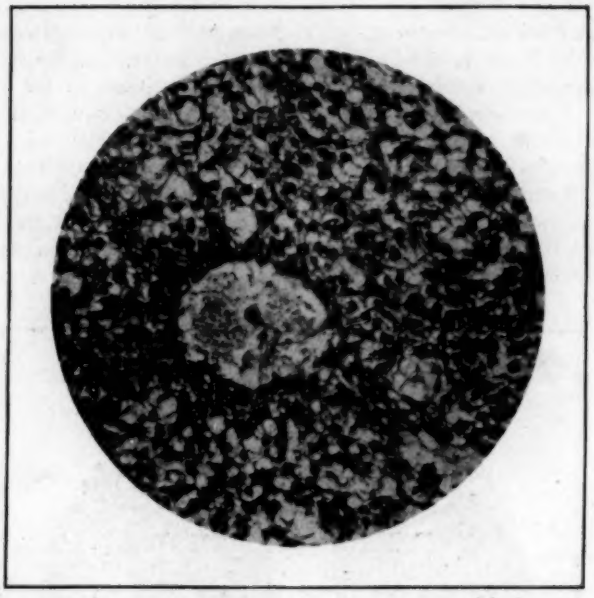

Fig. 8.—Lymphangioma growing near knee; × 150. There is formation of a lymph-vascular channel which is surrounded by a complicated meshwork of cells.

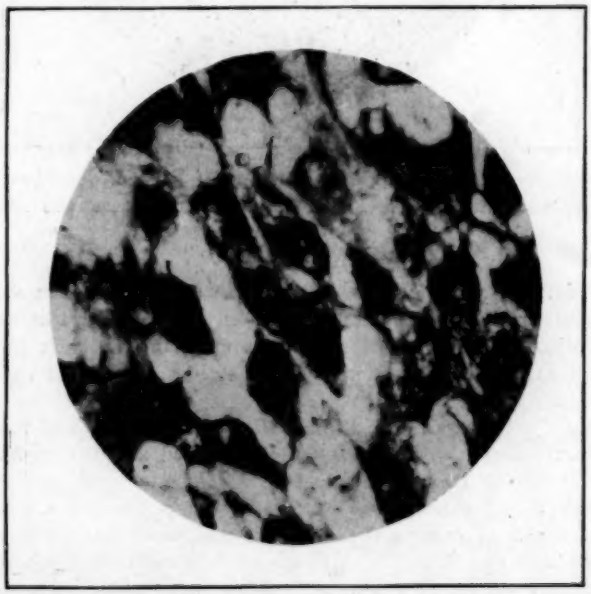

Fig. 9.—Lymphangioma growing near knee; × 800. The fine fibrillar processes of the cytoplasm forming connections with adjacent cells can be seen.

growth giving rise to metastases. The nature of the giant cells is still uncertain, and has been discussed elsewhere,[5] but they are probably modified endothelial cells as suggested by Mallory. Their absence from the metastases, in the present case, certainly suggests that they are not an essential constituent of the growth. The present case is of importance here as showing another example of a malignant "reticulo-endothelioma" and also as demonstrating that the almost invariably innocent "myelomas" of tendon sheaths may present malignant characters.

Further, it must be emphasized that no support has been found for the conception of the interchangeability of vascular endothelium and reticulo-endothelium as postulated by Foot. It seemed reasonable to expect that an innocent endothelial tumor would show such relationships more clearly than a malignant one

Fig. 10.—Malignant hemangioma in liver; × 100. Blood-vascular channels lined by a layer of flattened cells and surrounded by numerous small cells are shown.

on account of the less atypical character of the cells. This idea was confirmed by the examination of an innocent lymphangioma. The general appearances indicated the "reticular" character of those cells not immediately in relation to the channels (fig. 8), and detailed examination showed the origin of the fibrils from the tumor cells (fig. 9).

Similar relationships were found in a malignant hemangioma of the liver occurring in a woman, aged 58, in which the growth had almost completely replaced the right lobe of the organ. Figure 10 shows the general appearance of the growth, which varied a good deal in different parts. In some places the cells grew in flat sheets of cells, while in others they were less closely packed and gave rise to fibrils (fig. 11). In this case there seems to be very little doubt as to the possibilty of interchangeability of vascular endothelium and reticulo-endothelium.

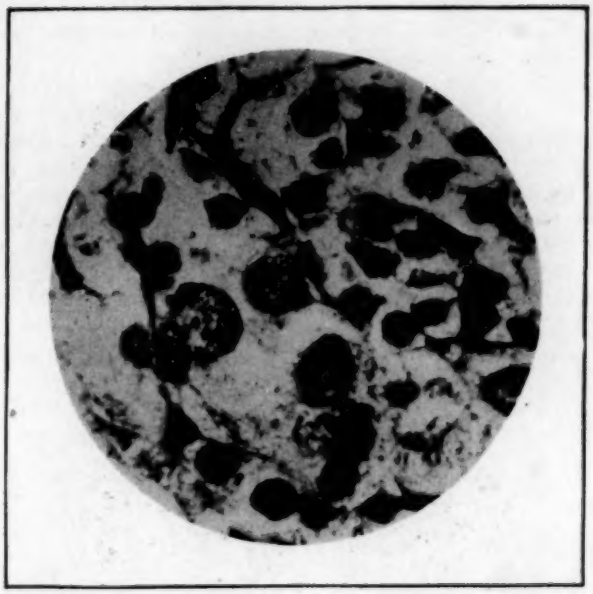

Fig. 11.—Malignant hemangioma in liver; × 800. The relationship of reticular fibrils to tumor cells is here similar to that seen in the other figures.

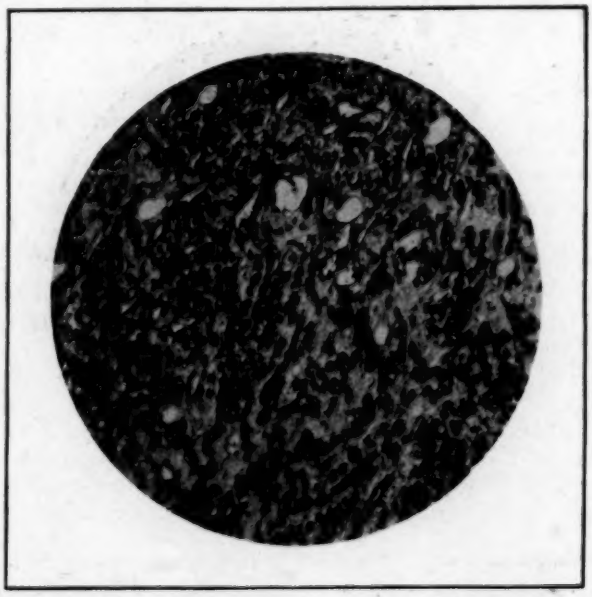

Fig. 12.—"Endothelioma" from buttock; × 150. The cells embedded in plentiful finely fibrillar stroma are seen.

Fig. 13.—"Endothelioma" from buttock; × 600. The close intermingling of cells and fibrils is obvious.

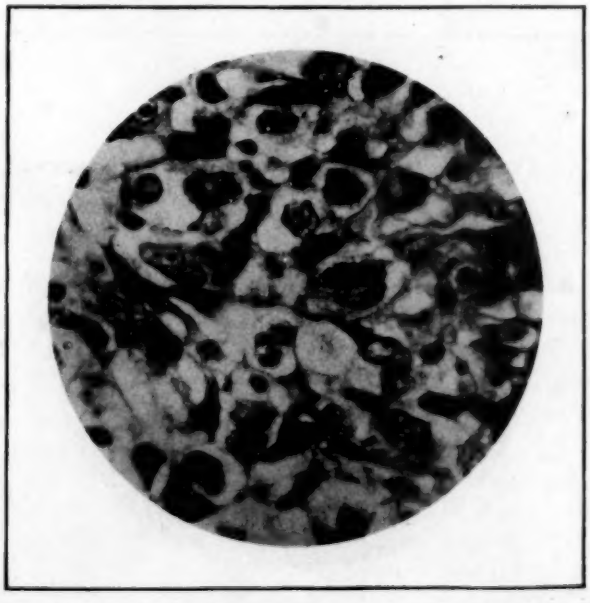

Fig. 14.—"Endothelioma" of bone; × 600. The cells of this actively growing tumor lie in a fine reticular stroma which seems to be nothing more than a special differentiation of the protoplasm of the cells.

Although the detailed consideration of the relationships of solid to vascular endotheliomas is beyond the scope of this paper, it is well to realize that no sharp separation is possible.

It is of interest to consider another case of solid endothelioma which arose in the buttock between the heads of the biceps. The histologic appearances were of the same general character as those already described, but, in quite a large number of places, there was excessive formation of reticular ground substance and paucity of cells, such as is seen in the "mesotheliomata" of the pleura and peritoneum, and differing from the "cylindromas" in showing no swelling or hyaline change of the fibrils (fig. 12). Such a case would seem to present particularly useful material in which to demonstrate the relationships of cells to fibrils. Figure 13 shows the apparent origin of the fibrils from the protoplasm of the tumor cells.

There seems to be no doubt that this tumor belongs to the same group as those previously described here, but it is not possible to demonstrate the nature of the tissue from which it has arisen.

The endotheliomas of bone are of importance here because no lymphatic channels are present in the bone marrow, and therefore endothelial growths there can arise only from the reticular supporting tissue or from blood channels. Figure 14 shows that whatever may be the site of origin of these tumors, they show the appearances of a "reticulo-endothelioma."

The "fibro-endothelioma" of the dura mater needs only to be mentioned, because its "fibrous" component is really only a special differentiation of the essential cells, that is, this is also a reticulo-endothelioma.

CONCLUSIONS

The series of neoplasms here discussed demonstrates that growths of "endothelial" character may present either the signs of vasoformative activity or of production of fibrils by differentiation of their protoplasm. Both phases of cell activity may be present in any one of the tumors, although, as a rule, one manifestation is the more obvious.

It is suggested that the term reticulo-endothelioma be used as a descriptive term applying to the growths in which fibril formation is a striking feature.

The mode of formation of fibrils is almost similar to that described by Corner as occurring in normal endothelium.

The histologic relationships of endothelioma, lymphosarcoma and Hodgkin's disease will be discussed later, but here it may be contended that the difference between these conditions is one of degree rather than of kind.

PATHOLOGIC CHANGES IN VOLUNTARY MUSCLE

I. DEGENERATION AND REGENERATION OF THE RECTUS ABDOMINIS IN PNEUMONIA *

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Since Zenker's [1] classical description of hyaline degeneration of voluntary muscle found in fatal cases of typhoid fever, which were studied during an epidemic in Dresden between 1859 and 1862, this form of pathologic alteration of striated muscle has been known as "Zenker's degeneration." Zenker himself, however, attributes the original description of hyaline degeneration of voluntary muscle in typhoid fever to Louis, whose work appeared in 1830, about thirty years before his own. Rokitansky mentioned rupture of the rectus abdominis muscle in typhoid in 1844, but it remained for Virchow to make the first detailed report of such a lesion.

Zenker found that the rectus abdominis muscle was most frequently the site of degenerative changes, but that many other muscles suffered in the course of the disease. Among these were the other muscles of the abdominal wall, those of the thigh, especially the adductor group, the diaphragm, the biceps brachii, pectoralis major, subscapularis, gastrocnemius and finally the tensor tympani.

In the 120 cases which were studied by Zenker, the muscular lesion was so constant that it was regarded as a significant manifestation of typhoid, and as such was given a place of considerable importance in the diagnosis of the disease. The muscular lesion as described consisted of hyalinization of the contractile substance of the muscle fiber, followed by complete or partial destruction of the muscle substance. As seen grossly, the muscle presented marked pallor and was found to be extremely brittle and friable. The latter properties often led to rupture of the muscle, which was followed by hemorrhage. Microscopically, the degenerative changes consisted of loss of striations of the fibers with clumping of the hyaline contractile substance, all of which was associated with destruction of the fibers, in toto or in part, and individually or in groups. Associated with these degenerative changes, regeneration of the muscle was observed in the form of nuclear proliferation followed by the development of new muscle fibers.

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1. Zenker: Veränderungen der willkührlichen Muskeln im Typhus abdominalis, Erlangen, 1863.

Within a period of five or six years following Zenker's publication, the problem of degeneration and regeneration of striated muscle was vigorously attacked by numerous workers, the more conspicuous of whom were Waldeyer,[2] Weber,[3] Hoffmann,[4] Neumann [5] and Janovitsch Tschainski.[6] Only one of these, Hoffmann, based his work on the muscle changes occurring as the result of a disease process. The typhoid epidemic of 1866, in Basel, furnished the material for his study. The other workers of this period pursued the subject entirely from an experimental standpoint and strove to coordinate their findings with those published in connection with the disease process in man.

The more recent investigations in connection with degeneration and regeneration of striated muscle have dealt with the muscle changes resulting from injuries, wounds, infections, invasion by tumors, etc.

In the fall of 1918, during the great influenza epidemic, exhaustive studies were made of the fatal cases of pneumonia among the troops in the United States Army camps. Among these cases were found a considerable number which presented definite lesions in the rectus abdominis muscle. The observed muscle changes as first mentioned by MacCallum [7] and later by Wolbach and Frothingham [8] and Goodpasture,[9] were essentially the same as those described in the older literature in typhoid fever, and consisted of hyalinization of the muscle with degeneration followed by conspicuous regenerative phenomena. Similar muscle lesions were found in fatal cases of secondary pneumonia, which were studied in the course of an epidemic of measles among the troops in the United States Army camps during the Great War. It is our purpose here to study the process of degeneration and regeneration of

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2. Waldeyer: Ueber die Veränderungen der quergestreiften Muskeln bei der Entzündung und dem Typhusprozess, sowie über die Regeneration derselben nach Substanzdefecten, Virchows Arch. f. path. Anat. **34**:473, 1865.

3. Weber: Ueber die Neubildung quergestreifter Muskelfasern, insbesondere die regenerative Neubildung derselben nach Verletzungen, Virchows Arch f. path. Anat. **39**:216, 1867

4. Hoffmann: Ueber die Neubildung quergestreifter Muskelfasern insbesondere beim Typhus abdominalis, Virchows Arch. f. path. Anat., Oct. 5, 1868.

5. Neumann: Ueber den Heilungsprozess nach Muskelverletzungen, Arch. f. mikroskop. Anat. **4**:323, 1868.

6. Janovitsch Tschainski: Ueber die entzündlichen Veränderungen der Muskelfasern. Studien aus dem Institute für experimentelle Pathologie in Wien, 1869.

7. MacCallum: Rockefeller Inst. for M. Res., Monograph No. 10, New York, 1919.

8. Wolbach and Frothingham: The Influenza Epidemic at Camp Devins in 1918. A Study of the Pathology of the Fatal Cases, Arch. Int. Med., Oct. 15, 1923, p. 576. Frothingham: Contribution to Medical and Biological Research, dedicated to Sir William Osler **1**:513, 1919.

9. Goodpasture: U. S. Naval M. Bull. 13, no. 2, 1919.

the rectus abdominis muscle as occurred in the materials obtained at necropsy of the cases of fatal pneumonia mentioned above. In connection with this, in order to throw more light on certain phases of the question, it has been necessary to undertake certain experimental procedures. These experiments are to be reported in a succeeding paper.[10]

MATERIALS STUDIED

The accompanying table gives in summary a list of twenty-five cases in all of which lesions were found in the rectus abdominis muscle. These lesions vary considerably in character in the different cases, the variation apparently being dependent on two factors: the duration of the disease and the intensity of the infection as observed clinically. The earliest change consists of a marked pallor of part or all of the muscle. This is found in one or both recti. There may be small, irregularly distributed foci in the muscle which have a grayish, translucent appearance, all of which represent hyalinization of the muscle substance. In more advanced cases large segments of muscle of one or both recti have this hyaline appearance. Associated with the massive or focal hyalinization is found an extraordinary fragility. This brittleness may be followed by rupture of the muscle with subsequent hemorrhage, resulting in a hematoma within the sheath of the rectus. In cases in which organisms were present in the blood stream, the hematoma became infected, leading to abscess formation within the abdominal wall. Rupture is the more frequent sequel of the degenerative changes, having been found in seven of the cases, while abscess formation occurred in only one. In one of the rupture cases, however, organisms (*Streptococcus hemolyticus*) were found in the bloody fluid from the muscle and at the same time in the heart blood. Nineteen of the twenty-five cases were cases of secondary pneumonia following influenza. In every case the lung lesion was either a characteristic lobular type of consolidation or the peculiar interstitial bronchial type which has been described in detail by MacCallum, Wolbach and Frothingham, and others. Only two of the cases followed pneumonia secondary to measles. One of these was an atypical case, probably German measles. The pneumonia, however, was of the interstitial type. The remaining four cases were either primary lobular consolidation of the lungs or interstitial bronchial pneumonia without preceding disease of any sort. In all cases the muscle affection arose as a complication of the pneumonia and apparently had no connection with the preceding measles or influenza.

Accurate bacteriologic studies were not possible in all cases, although attempts were made at every necropsy to determine the etiologic agent

10. Forbus: Pathological Changes in Voluntary Muscle. II. Experimental Study of Degeneration and Regeneration of Striated Muscle with Vital Stains, Arch. Path., in press.

Case No.	Anatomic Diagnosis	Duration of Disease	Etiologic Agent	Time Between Death and Necropsy
81*	Bilateral organizing disseminated interstitial bronchopneumonia; moderate degeneration of rectus abdominis muscle	19 days	Bacillus influenzae.....	2 hours
80*	Bilateral interstitial organizing pneumonia; embolism of pulmonary artery; hyaline degeneration of rectus abdominis muscle with hemorrhage	15 days	Bacillus influenzae.....	3 hours
82*	Bilateral confluent lobular pneumonia; rupture of rectus abdominis muscle with hemorrhage	16 days	Pneumococcus	2 hours
86*	Disseminated interstitial bronchopneumonia; hemorrhagic areas in rectus abdominis muscle; subacute endocarditis	20 days	Bacillus influenzae.....	1 hour
87*	Bilateral interstitial bronchopneumonia; empyema; pericarditis, endocarditis, myocarditis; fibrous orchitis; acute splenic tumor; infarcts in spleen and kidney; bilateral abscesses of rectus abdominis	21 days	Pfeiffer bacillus; pneumococcus IV (in lungs and muscle abscess); Staphylococcus albus	4 hours
88*	Interstitial bronchopneumonia with fibrinopurulent pleurisy; hemorrhagic necrosis of myocardium of left ventricle; bilateral ruptured rectus abdominis with hemorrhage	15 days	Pneumococcus (blood culture); Bacillus influenzae (lung)	4 hours
89*	Bilateral disseminated interstitial bronchopneumonia; pleural adhesions; acute fibrinopurulent pericarditis; marked pallor of upper segment of rectus abdominis	15 days	Bacillus influenzae; Streptococcus hemolyticus	5 hours
181†	Lobular pneumonia; ulcerative laryngitis; interstitial bronchopneumonia; small areas of degeneration in rectus abdominis	11 days	Streptococcus hemolyticus; Staphylococcus aureus (both cultured from sputum)	38 hours
220*	Bilateral lobular pneumonia; tuberculosis of lung, liver and spleen; hyperplasia of bone marrow; focal degeneration of rectus abdominis	15 days	Pneumococcus IV (blood culture)	11 hours
221*	Bilateral confluent lobular pneumonia; ulcerative laryngitis; hyaline degeneration of rectus abdominis	11 days	Pneumococcus IV; staphylococcus (both in lung culture)	7 hours
222*	Bilateral confluent lobular pneumonia; hyaline degeneration of rectus abdominis	Undetermined	Pneumococcus IV.....	14 hours
225*	Bilateral confluent lobular pneumonia; pleural adhesions; horseshoe kidney; hyaline degeneration of rectus abdominis	7 days	Pneumococcus IV (blood culture)	2 hours
226*	Bilateral confluent lobular pneumonia; beginning degeneration of rectus abdominis	Undetermined	Pneumococcus, staphylococcus, streptococcus, (lung culture)	Unknown
229*	Chronic endocarditis; mitral stenosis; confluent lobular pneumonia; early degeneration of rectus abdominis	10 days	Pneumococcus IV.....	25 minutes
230*	Bilateral confluent lobular pneumonia; fibrinous pleuritis; ulceration of vocal cords; beginning degeneration of rectus abdominis	6 days	Pneumococcus IV.....	4 hours
6152	Lobular pneumonia, left lung, with abscess; splenic tumor; emphysema; early degeneration of rectus abdominis	4 days	Streptococcus hemolyticus	Unknown
187‡	Lobular pneumonia; rupture of rectus abdominis	11 days	Streptococcus hemolyticus (blood and fluid from rupture of muscle)	14 hours
188†	Bilateral lobar pneumonia; acute nephritis; fibrous pleuritis; hyaline degeneration of rectus abdominis	11 days	Pneumococcus	2 hours
193‡	Interstitial bronchial pneumonia; rupture of rectus abdominis; fibrinous pleuritis	11 days	Streptococcus hemolyticus (blood culture)	21 hours
205¶	Interstitial bronchial pneumonia; empyemia, suppurative otitis media; bilateral rupture of rectus abdominis	16 days	Pneumococcus; streptococcus hemolyticus (blood); culture from muscle sterile	12 hours
212*	Lobular pneumonia with purulent pleurisy; acute splenic tumor; hyperplastic bone marrow; hyaline degeneration of rectus abdominis	9 days	Pneumococcus I (blood culture)	17 hours
215*	Bronchial pneumonia; fibrinopurulent pleurisy; ulceration of vocal cords; hyaline degeneration of rectus abdominis	10 days	Bacillus influenzae; pneumococcus	5 hours
217*	Confluent lobular pneumonia; pseudomembranous laryngitis; emphysema; bilateral degeneration of rectus abdominis	14 days	Pneumococcus	6 hours
218*	Bilateral confluent lobular pneumonia; focal degeneration of rectus abdominis	23 days	Pneumococcus IV (blood culture)	3 hours
219*	Confluent lobular pneumonia; emphysema; granular degeneration of fibers of rectus abdominis	10 days	Streptococcus hemolyticus (blood culture)	20 hours

* Influenza.
† No measles or influenza
‡ German measles.
¶ Measles.

in connection with the lung infection. In ten of the cases the pneumonia was unmistakably due to the pneumococcus, type IV predominating. These organisms were isolated in pure culture from the lungs in some cases and from the heart blood in others. *Streptoccocus hemolyticus* was found responsible for the pneumonia in four cases, these organisms being found in pure culture, either in the lungs only or in the lungs and heart blood. *Bacillus influenzae* alone was cultured from the lungs or heart blood in three cases. A mixture of organisms seemed to be responsible for the remaining eight. In all, however, one or all three of the organisms mentioned above were found in cultures from the heart blood or lungs or, in one case, in the muscle lesion itself.

It is obviously impossible to arrive at any conclusion regarding the specific cause of the muscle lesion. In one case in which an abscess was present in the muscle, pneumococcus type IV was cultivated directly from the lesion. This organism was likewise found predominating in a mixture of staphylococcus and *Bacillus influenzae* in the lungs. In none of the other cases could the presence of bacteria be demonstrated in the muscle lesion, though organisms were cultured from the heart blood. The absence of bacteria from the field of degeneration in the muscle is in accord with the peculiarity of the lesion, which, as will be seen later, is unlike an acute inflammatory process.

The duration of the pulmonary process gives no aid in the search for a specific cause of the muscle degeneration. In one case the pneumonia lasted only four days. This was sufficient time for the development of early degenerative lesions in the rectus muscle. This was one of the *Streptococcus hemolyticus* cases, but no organisms were found in the muscle. The other extreme is represented by a twenty-three day type IV pneumococcus infection in which early focal changes were found in the muscle in the absence of any organisms. Thirteen days of acute pulmonary infection proved ample for the development of the muscle lesion, as shown by the average duration in all cases. Some cases of the average duration showed only slight pathologic changes, while others presented most extreme alterations. The intensity of the infection seems to offer the better explanation of the variation in the muscle condition.

Because of the absence of bacteria from the muscle lesion, and in view of the peculiar noninfective character of the lesion, one is forced to look elsewhere than to direct bacterial infection for the explanation of the degeneration of the muscle. The most natural direction to turn under these circumstances is to some theoretical toxin which may be elaborated by the organisms concerned in the pulmonary disease. The apparent coordination between the intensity of the infection clinically and the degree of damage to the muscle mentioned above, lends support to this idea. On the other hand, the fact that only the rectus abdominis muscle is affected in these cases seems weighty argument against a toxic

action unless one feels at liberty to attribute some theoretical specificity to the toxic substance or some peculiar susceptibility to the rectus abdominis muscle, either of which cannot be more than mere speculation. In typhoid fever the rectus abdominis is only one of many muscles

Fig. 1.—Hyaline degeneration of rectus abdominis muscle in pneumonia. Characteristic clumps of hyaline contractile substance surrounded by phagocytic cells. Longitudinal splitting of old fibers as seen in the center where new muscle nuclei are numerous. Vacuolization of one of the larger swollen and partially degenerated fibers is seen just below the center of the photograph.

affected, as was noted by Zenker. Such widespread lesions as were found in his cases suggest strongly a toxic origin. In our own cases of pneumonia, however, consistent search for lesions in other muscles than the recti were fruitless, and so we hardly have the theoretical toxicity idea to fall back on in hunting for an explanation of this unusual condition.

DEGENERATION

The gross appearance of the damaged muscle has been described above. It remains now to give the microscopic details of the degenerative process which produces such extraordinary alterations of the muscle substance.

Apparently the primary change in the muscle fiber expresses itself in the form of a swelling of the contractile substance, which may be quite uniform throughout a single fiber or quite localized involving only short segments of the fiber. In a whole microscopic field only a single fiber may be affected, or a single focus in one fiber may alone give evidence of the pathologic alteration. The nature of the sarcolemma and muscle nuclei, as well as the specific character of the cross and longitudinal striations, does not seem to vary from the normal in this stage of the process of degeneration. Changes in these structures, however, follow quickly the initial swelling of the fiber.

Even before the succeeding alteration in the contractile substance, which appears very soon after the swelling of the fiber, a remarkable nuclear activity is observed within the affected fiber. These nuclei increase in number to such an extent that they sometimes fill the sarcolemma sheath. They follow a fairly definite arrangement in their distribution. They may be just beneath the sarcolemma or deeply embedded in the contractile substance toward the center of the fiber. They are always arranged in rows closely packed together, the long axis of the line of nuclei always parallel to that of the affected fiber. Rarely if ever does one see mitotic figures during this initial nuclear proliferation. The process seems to be wholly amitotic. Nuclei with constrictions, sometimes as many as three, are not infrequent. Although these nuclear changes are usually preceded by the increase in diameter of the fiber due to swelling, there are many instances in which the nuclear proliferation furnishes the first evidence of any damage to the fiber. An injured fiber may be readily detected in a field of otherwise normal muscle by this striking feature.

Fibers which show the swelling and nuclear proliferation described above undergo a rapid degeneration which leaves them in a most useless state. The contractile substance loses its striations. The cross striations disappear first and are soon followed by the longitudinal striae, leaving the body of the fiber in the form of an amorphous mass of homogeneous material which has a waxy, translucent, highly refractile appearance in

the gross, and which when stained may be recognized as characteristic hyaline.

This homogeneous appearance of the hyaline contractile substance does not persist for any length of time. Vacuoles appear, giving evidence of a dissolution of the degenerated material. These vacuoles are sometimes filled with fat, and apparently represent the results of some chemical as well as physical alteration of the hyaline substance. Another change in the character of the hyaline contractile substance which one

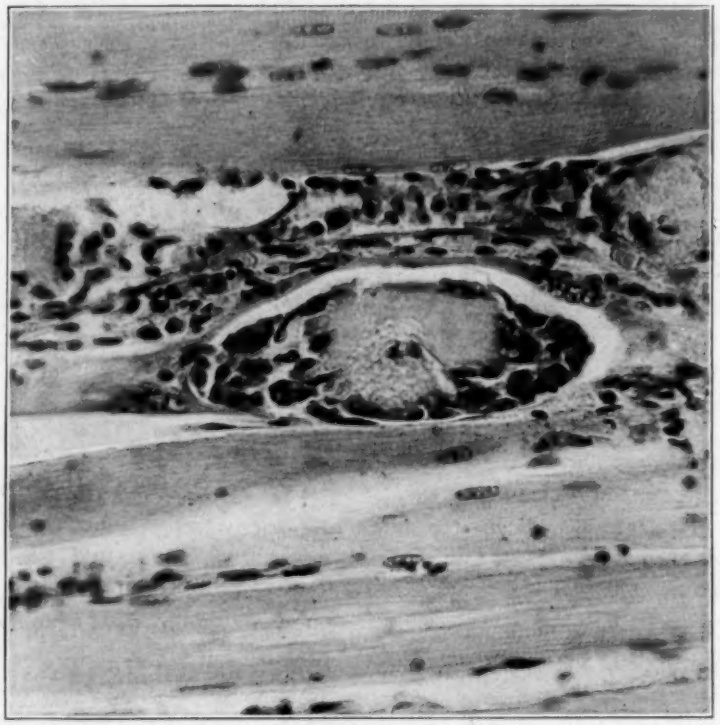

Fig. 2.—High power magnification of one of the clumps of hyaline contractile substance from degenerated rectus abdominis. Two general types of cells are distinguishable: those with pale nuclei and indefinitely outlined cytoplasm, and those with deeply stained nuclei and definitely outlined cytoplasm, the former muscle cells and the latter phagocytic cells of extramuscular origin. Cross and longitudinal striations are still present in the adjacent fibers although one of these is in process of degeneration, as shown by its vacuolated appearance.

may see is the separation of the homogeneous mass into granules of varying degree of fineness. This granular type of degeneration is entirely different, however, from a form of degeneration of muscle substance found in some of the cases in which the postmortem examination had been made some hours after death and in which postmortem

autolysis had begun. A true granular degeneration of the contractile substances, not preceded by homogeneous hyalinization, as described by Volkmann [11] in typhoid fever, we have not succeeded in finding. In every case in which this form of change in the fiber has been conspicuous we have been able able to coordinate with it an unusually long interval between the necropsy and the death of the patient. A more weighty argument against this form of degeneration in our cases is found in the complete absence of any nuclear changes in the affected fiber, a thing which is almost never seen in the fibers which show the usual hyalinization.

The fate of the sarcolemma in this destructive process has always been a problem of considerable interest and importance. Some of the earlier workers, among whom were Hoffmann [4] and Kraske,[12] maintained that this structure was completely destroyed and that a new muscle fiber sheath arose in connection with the subsequently regenerating fiber. Hoffmann studied hyaline degeneration in typhoid fever, while Kraske's work was entirely experimental. Contrary to this view, Volkmann,[11] who also studied typhoid muscle, insisted that the sarcolemma remained undisturbed in the true hyalinization process, and considered this feature an essential requisite for the proper development of the regeneration of the fiber which follows. In our own material, the persistence of the sarcolemma is inconstant. In the earlier changes of the muscle fiber, even after complete hyalinization and clumping of the contractile substance, the sarcolemma may still be seen clearly. This delicate membrane forms a retaining sheath which confines the degenerated material to a restricted zone. The persistence of the sarcolemma makes possible the formation of the much discussed "Muskelzellenschlauche" which Waldeyer [2] described in 1865. On the other hand, there is no doubt that in some locations in which the muscle degeneration is extreme, the sarcolemma suffers destruction along with the contractile substance. In any case there must occur breaks in this sheath to facilitate the incoming of the cells which will be seen later to be essential to the repair of the degenerated fiber. However, one is impressed by the remarkable resistance which this part of the muscle fiber offers to destructive agencies. The reaction of the contractile substance furnishes a striking contrast.

Destruction of the muscle fiber may follow a materially different course from that outlined above. The initial swelling of the fiber with loss of striations and nuclear proliferation may be seen as usual. Succeeding this, however, the fiber splits along its longitudinal axis into

11. Volkmann: Ueber die Regeneration des quergestreiften Muskelgewebes beim Menschem und Säugetier Beitr. z. path. Anat. u. z. Allg. Pathol. **12**:233, 1893.

12. Kraske: Experimentelle Untersuchungen über die Regeneration der quergestreiften Muskeln, Habschr., Halle, 1878.

numerous bands, each one of which contains an unusual number of nuclei. The line of cleavage is usually found at the site of the extraordinary nuclear proliferation. This is so striking in some places that it is more than suggestive that the splitting of the contractile substance is a consequence of the pressure of the large number of newly formed nuclei. The steps which follow in the disintegration of the fiber substance are essentially the same as already described. The contractile substance becomes a mass of hyalin which is similar in every way to

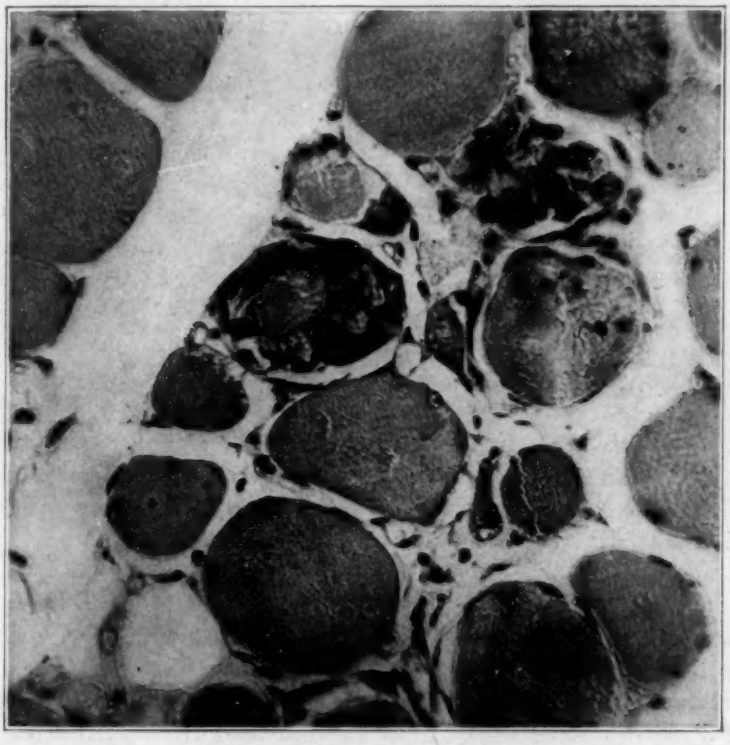

Fig. 3.—Cross section of degenerating rectus abdominis. New muscle cells and phagocytic cells surround the mass of hyaline contractile substance.

the hyaline clumps found in the fibers which have undergone no longitudinal splitting. In this form of degeneration the sarcolemma must necessarily undergo destruction.

The splitting of the fiber which has just been described is of considerable importance because it is in the interpretation of this picture that much confusion and difference of opinion is to be found. Neumann [5] and Nauwerck [13] believed it to be a form of regeneration of the muscle from the old intact fiber. Felix already had shown that

13. Nauwerck: Ueber Muskelregeneration nach Verletzungen, Jena, 1890.

such a type of muscle formation was common in embryonic life. Kraske, on the other hand, looked on these numerous muscle bands and ribbon-like muscle plates as remains of the old fibers. That this arrangement of the muscle substance should be so differently interpreted is easily understood, for in the absence of any absolute test it is most difficult to distinguish between the ribbon-like muscle segments of the old fibers and the almost similar bands of newly formed muscle.

When a hematoma develops in the muscle as a result of rupture of the previously damaged muscle substance, the features observed in connection with the muscle fiber are not different from those already described. The hemorrhage is simply a secondary manifestation. Bacterial infection of the muscle, however, which leads to an acute inflammatory reaction or even abscess formation as occurred in one of our cases, produces a clear-cut difference in the appearance of the muscle. If no hyaline degeneration of the sarcoplasm has preceded the invasion of bacteria, none of the degenerative changes which we have described are found. In place of the muscle changes usually seen, one finds a wholesale death of tissue which involves all the components of the muscle. The muscle substance is represented by a necrotic mass packed with leukocytes and mononuclear wandering cells. Quantities of bacteria may be demonstrated in the tissue. About the edges of the infected area the muscle fibers may retain their form, but the nuclei do not stain; the contractile substance, although retaining its striations, is atypical in its staining reaction. Nowhere is there any evidence of nuclear activity. The general condition of the muscle is therefore found to be quite different from that which we have described as "hyaline degeneration."

In the degenerative process the supporting tissue of the muscle seems to have no place. The endomysium and perimysium appear in their normal relationship to the degenerated muscle fibers and the muscle bundles, respectively. In cross-sections of the degenerated muscle the fine fibrous tissue network can be demonstrated in beautiful contrast to the sarcolemma sheaths which persist. Where the latter have been destroyed, the endomysium forms a retaining membrane for the hyaline contractile substance and the newly formed muscle nuclei.

Blood vessels and nerves occupy a position during the degeneration of the muscle similar to that of the connective tissue. The vascular bed surrounding the muscle fiber undergoes no conspicuous alteration except when there is rupture of the muscle. The nerve fibers remain as in the unaffected muscle. The method of preservation of our material has rendered it unsuitable for detailed study of the nerve endings. So far as we have been able to see, however, without the use of special technic, these structures have undergone no obvious alterations except so far as they disappear in the course of destruction of the sarcolemma.

THE REPAIR PROCESS; REGENERATION

The degeneration of the rectus abdominis muscle has been seen to leave the muscle in a seriously affected condition so far as any muscular function is concerned. The muscle, were it to remain in such a state, would be impaired in its usefulness to a degree commensurate with the extent of the degeneration. This loss of substance, subsequent to any other cause than that which operates in such a condition as we have under consideration, would be followed by a repair process in which connective tissue would play the dominant rôle, producing in the place

Fig. 4.—Degenerated rectus abdominis, longitudinal section. In the center is a new muscle fiber in process of development from muscle spindle cells. Just above this and adjacent to hyaline contractile substance are other new muscle cells. Longitudinal striations can be seen under the microscope in these newly developing forms. No cross striations can be made out.

of the destroyed muscle a nondescript type of scar. Extensive injuries to voluntary muscle accompanied by loss of tissue have been known to heal always by scar formation. Indeed, according to Volkmann's work,[11] there is at best only partial restoration of destroyed muscle tissue, no matter what the agent of destruction may be, except in the damage which is done in typhoid fever and conditions of allied nature. However,

at this point we must refer to some recent work on regeneration of muscle following the production of large muscular defects by excision. This work is reported by Bier,[14] Martin,[15] and Bundschuh,[16] all apparently having used the same method in their experiments. Defects in the muscle substance were allowed to fill with serum or were filled with salt solution, and allowed to heal. Bier claims complete restoration of the muscle, while Bundschuh found that there was much scar tissue responsible for the filling up of the tissue defect. Bier based his conclusions partially on clinical data, which it would seem could be controlled only with greatest difficulty. This probably accounts for the discrepancy in his results and those of Martin and Bundschuh who used Bier's own method in their experiments.

In the edges of defects produced in muscle by excision, practically all of those who have experimented with regeneration have observed some new muscle formation. We have always seen it in our own experiments, but in no case have we met with total restoration of the muscle in artificially produced muscle destruction. Contrary to this, in the repair process which succeeds hyaline degeneration of muscle in pneumonia, as in typhoid fever, the evidence is indicative of complete regeneration of the affected muscle, except in those cases in which large defects occur as a result of the formation of hematomas or abscesses. The details of this restoration of the muscle to normal we have observed as follows.

During the period of hyalinization and necrosis of the degenerating muscle, important steps are in progress within the sarcolemma which facilitate repair of the degenerated muscle. Every hyaline clump becomes surrounded by a mass of cells which rapidly envelop the dead contractile substance. The intact sarcolemma filled with the cells which are responsible for the removal of the hyaline débris from the field of operation and the newly formed muscle cells to be described later, constitutes the "Muskelzellenschlauche" of Waldeyer.[2] The analysis of this formation has served since Waldeyer's paper, or, as a matter of fact, since Zenker's original description of degeneration, as a source of constant argument. Since Waldeyer centered the attention of the students of regeneration on this collection of cells, not one has failed to attack the problem of differentiation of the cells that compose it, and not one has come to a satisfactory conclusion regarding their origin.

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14. Bier: Deutsche med. Wchnschr. 48, nos. 1 and 2, 1917.

15. Martin: Regeneration quergestreifter Muskeln, Arch. f. klin. Chir. **111**: 673, 1919.

16. Bundschuh: Ueber die Regeneration des quergestreiften Muskels, Beitr. z. path. Anat. u. z. allg. Pathol. **71**:674, 1923.

Morphologically and by differential staining, the cells lying within the sarcolemma may be shown to be of the following types: (1) leukocytes, (2) lymphocytes, (3) plasma cells, (4) large mononuclear phagocytic cells, (5) large multinucleated phagocytic cells, (6) muscle spindle cells, and (7) large multinucleated muscle syncytial masses.

There is, of course, no problem connected with the leukocytes, lymphocytes and plasma cells. The first two are blood elements and wander into the affected area just as they do as a result of any tissue injury. Leukocytes are conspicuously scarce, their presence being unusual except in cases in which the zone of degeneration is infected. They appear therefore to be incidental and are not a characteristic part of the picture. The phagocytic activity of these cells is not striking. The lymphocytes are somewhat similar to the leukocytes in their relation to the general repair process. They are more numerous but seem to occupy a position of little significance. Plasma cells are still more frequently seen. They are more numerous, however, in the interstitial tissues than within the sarcolemma sheath. Their presence, similar to that of the leukocytes and lymphocytes, seems to be of little importance.

The phagocytic cells of both varieties, mononucleated and multinucleated, present a most interesting problem from the standpoint of their origin. Their physical characteristics may be briefly summarized as follows:

1. Nucleus: quite large and comparatively compact; may be single or multiple; chromatin rather scant and present in the form of coarse granules; position in cytoplasm not constant; nucleolus practically always absent; occasionally seen in mitosis.

2. Cytoplasm: abundant, whole cell about three times the size of a leukocyte; structure finely granular; sometimes vacuolated, and frequently seen with destroyed material ingested; cell membrane very indistinct.

These cells show no special characteristics when stained with hematoxylin and eosin. If, however, one uses Wright's blood stain, they stand out in fairly definite contrast to the leukocytes, plasma cells and lymphocytes. With this stain alone, however, they cannot be differentiated from the muscle cells which are present in the form of the large multinucleated syncytial masses. The nucleus with this stain seems more compact than with the ordinary hematoxylin and eosin, but the character of this reaction is not sufficient to do more than help in the matter of differentiation. The cytoplasm stains rich purplish blue in striking contrast to the bright red or pink of the normal or hyaline contractile substance. This reaction of the cytoplasm is not specific for these cells, but seems to be characteristic for all actively changing cytoplasmic substance. The delicate, newly formed cytoplasm of the muscle cells which can barely be distinguished with hematoxylin and eosin stands out brilliantly with the Wright stain. It is obvious, there-

fore, that the phagocytic cells cannot be distinguished from the muscle cells on the basis of staining reaction alone. Morphologically, the two types are further apart; but this feature alone is not sufficient for differentiation. The two taken together form strong evidence, however, that the phagocytic cells and the muscle cells are entirely different in character and in origin. The phagocytic cells are seen in varying numbers in the supporting tissue of the muscle and especially along the walls of the smaller vessels, all of which, together with their outspoken phagocytic character, speak for an extramuscular origin and would lead one to consider them most probably mononuclear wandering cells and not cells derived from the muscle nuclei. We have gained material support for this view by a series of experiments which are reported in a separate paper.[10] In experimental degeneration and regeneration there seems to be satisfactory proof that these cells do wander in and have no original connection with the muscle fiber itself.

Zenker [1] observed the striking accumulation of cells in the damaged muscle and regarded this cellular proliferation as a part of the reaction of the perimysium internum. He made no special effort to differentiate between the phagocytic cells and the cells giving origin to the new fiber. Waldeyer,[2] who originally centered attention on the collection of cells within the sarcolemma, believed that the majority of the cells of the "Sarcolemmschlauche" were of muscular origin, but would not deny that other cells may come from without the sarcolemma though he did not say whence. Weber [3] went so far as to question the specificity of adult tissues, and stated that the muscle cells may produce the "pus cells" which he found in the sarcolemma. This view was somewhat emphasized by Hoffmann,[4] who believed that "inflammatory cells" might be derived from muscle cells. Gussenbauer [17] was the first to put forward valid arguments for the extramuscular origin of the phagocytic cells of the sarcolemma. He showed by animal experiments that the accumulation of cells takes place before there is sufficient time for the development of the muscle cells. He always found white blood cells and other recognizable wandering cells in the degenerated fiber within the first twenty-four to seventy-two hours following injury. He attributed the phagocytosis of the necrotic contractile substance entirely to these cells of extramuscular origin. An attempt was made to differtiate the purely phagocytic cells from other cells of the sarcolemma by vital staining by Janovitsch Tschainski.[6] Aniline dyes were injected intravenously during the course of injury and repair of the muscles. The cells surrounding the hyaline clumps were found loaded with ingested dye, but the experiments were apparently not pursued far

17. Gussenbauer: Ueber die Veränderungen des quergestreiften Muskelgewebes bei der traumatischen Entzündung. Arch. f. klin. Chir. **12**:1011, 1871.

enough to lead to any conclusions regarding the different types of cells. This writer contented himself with stating that he did not dare say that the cells of the sarcolemma had their origin from the blood cells simply because of their ability to take up the intravenous dye. Kraske [12] was able to differentiate "white blood cells" from "muscle cells" on a purely morphologic basis. The lead of Janovitsch Tschainski was followed by Kiyono,[18] who repeated the vital staining method, using carmine. Thus he was able to differentiate two types of cells—one phagocytic and the other without ability to take up the dye. The latter he believed to be the true muscle cells. In conclusion, however, he would not say that it was impossible for some of the "muscle cells" to become free and assume a phagocytic rôle. In Wolbach and Frothingham's [2] study of muscular degeneration in pneumonia, the cells of the sarcolemma sheath are regarded as either phagocytic wandering cells or as nonphagocytic muscle cells, the latter of muscular origin.

There is, therefore, no uniformity of opinion regarding the origin of the phagocytic cells of the "sarcolemmschlauche." Our own experiments,[10] however, which were carried out by use of the vital dyes, lead us to the view that at least in experimentally produced muscle degeneration and regeneration the cells which are responsible for the removal of the hyaline débris are of extramuscular origin.

It is difficult to say what becomes of the many phagocytic cells. It is clear that some die and undergo disintegration. There is good evidence for this in the altered character of their cytoplasm, the atypical staining reaction of the whole cell and the accumulation of fat droplets in the cytoplasm. Others, however, having engorged themselves with the hyaline débris, wander out into the interstitial spaces of the muscle tissue and eventually disappear from the field.

As we have described, the removal of the useless degenerated material from the affected fiber proceeds in an orderly way and at an unusually rapid rate. Long before the field has become clear, however, the activity of the muscle cells which have developed from the muscle nuclei becomes conspicuous, and the development of the new fiber early becomes evident. It is to this development that we now turn as the final phase in the restoration of the muscle fiber to its normal state.

The extraordinary nuclear proliferation which we have previously described as observed in the old damaged muscle fiber, and which occurs synchronously with the degenerative alterations in the contractile substance of the fiber, is the first evidence of regeneration. In actuality, then, the body may begin its repair process before the muscle fibers gives any very obvious evidences of damage to the contractile substance.

The new nuclei have two possible sources: first, the sarcolemma

18. Kiyono: Die Vitale Karminspeicherung, Jena, 1914.

nuclei and, second, the "muscle nuclei." The former are always at the periphery of the fiber, and in cross-sections appear to form a part of the sarcolemma. The latter are found embedded in the sarcoplasm, and apparently have no connection with the sarcolemma. In longitudinal sections of normal muscle, differentiation between these two types of nuclei is difficult. In shape and size they are similar. They differ somewhat, however, in their chromatin content and its distribution. The muscle nuclei do not contain as much chromatin, and therefore are clearer than the sarcolemma nuclei. In the latter the chromatin is abundant and exists in the form of rather coarse granules. The muscle nucleus always shows one conspicuous nucleolus and usually two, one at either pole. Nucleoli are quite inconstantly seen in the sarcolemma nucleus. The greater part, if not all, of the nuclear production in the damaged fiber arises in connection with the muscle nuclei. This view is supported by the fact that in advanced degeneration in which the contractile substance is found in clumps, and the spaces between clumps filled with newly formed cells, the sarcolemma appears absolutely unaltered, and its nuclei give no indication whatever of proliferation.

The muscle nuclear reproduction is apparently by direct division. The formation of muscle cells from these nuclei represents the second phase in the repair process.

The muscle nuclei are soon transformed into muscle cells by the accumulation of a cytoplasmic mass the source of which seems pretty clearly to be the undamaged sarcoplasm of the old fiber. The formation of these muscle cells is seen most clearly in the stump of old partially degenerated fibers. Here a club-shaped swelling occurs, which is composed of a mass of rather homogeneous glassy substance in which longitudinal streaks persist suggestive of old longitudinal striations. No cross striations are present. This substance is in every way similar to the delicate sarcoplasm of the normal fiber, and seems to be identical with it since a continuity with the sarcoplasm of the well preserved portion of the fiber is demonstrable in sections. The only difference apparently between the clubbed altered end of the old fiber and the well preserved fiber lies in the loss of cross and longitudinal striations and the great increase in the amount of the sarcoplasm. There is always a concentration of newly formed muscle nuclei in the clublike stump. Following the formation of the multinucleated terminal swelling of sarcoplasm the muscle nuclei individually or in groups of two or three appropriate to themselves some of the sarcoplasm, and thus muscle cells of two general types arise, i. e., large mononuclear cells with definite outline and large multinucleated muscle cells or syncytial masses. So far as we have been able to see, the mononuclear muscle cells as well as the large syncytial masses may lose their continuity with the old fiber, and therefore do not always represent a true sarcoplasmic bud as

described by some of the older writers. In serial sections one may usually demonstrate a direct contact between the newly formed muscle cells and the stump of an old fiber, but in numerous instances, if not in all, the individuality of the cell can be made out by a rather definite line of demarcation between undifferentiated sarcoplasm of the fiber stump and the cytoplasm of the cell body.

The formation of the muscle cells proceeds rapidly, leading to their presence in such large numbers as to fill partially the sarcolemma.

Lying along the intact sarcolemma but well separated and easily distinguished from it may be seen these same muscle cells, which have, however, undergone considerable alteration in size and shape, and now present themselves as spindle cells with elongated nuclei whose pointed ends may be entirely free from any connection with remains of the old fiber stump. These cells may be wedged in between hyaline contractile substance and the sarcolemma. They are sometimes surrounded by groups of phagocytic cells, in which case their outlines are made out only with considerable difficulty. These cells do not stain specifically but may be easily differentiated from the surrounding phagocytic cells on the basis of morphology alone. Growth changes appear rapidly. Some of the nuclei are seen in mitosis, while in other cells nuclear division has gone on rapidly leaving each cell with multiple nuclei. At the same time, the cytoplasm increases in amount and the size of the cell becomes greater and greater. When nuclear division has progressed to the extent where three to five nuclei appear in a single cell, very fine longitudinal striations appear in the cytoplasm. The cross striations apparently are an evidence of maturity of the fiber, and hence do not appear until very late. In fact, in none of our material have we been able to find newly formed muscle with definite cross striations. Nuclear proliferation and increase in size of the new muscle element continue until a sufficient length is attained to bridge the gap in the old fiber which resulted from the preceding degeneration. The diameter of the new fiber also increases. Whether this eventually attains proportions sufficient to fill the entire space within the old sarcolemma is doubtful; certainly in none of our material have we met with newly formed fibers of such a diameter. All of the most advanced new fibers which we have seen have a diameter not exceeding two or three nuclei. It is possible that two or more of these narrow new fibers may fuse to form a single fiber equal in size to the original. There seems to be little question about the development of more that one of the primitive spindle cells, for these cells are numerous within the sarcolemma. However, the condition of some of the early muscle cells indicates that a large number must undergo degeneration. It is obvious that should they all individually develop new fibers, a massive muscle tumor would be produced which would far exceed the limited demand for simple restoration of the

degenerated muscle. This has been spoken of at length by Neumann,[5] Nauwerck [13] and others of the older writers who argued strongly against the regeneration of the muscle from the isolated muscle spindle cells and held firmly to the budding method of regeneration.

What we have just described is in marked contrast to the budding process which Neumann and Nauwerck described at great length in connection with artificially produced muscle regeneration. These authors believed that there was an actual budding of the contractile substance of the old fiber at the juncture between viable sarcoplasm and hyaline contractile substance. They describe club-shaped masses of sarcoplasm in this location which they considered indicative of active growth of the old fiber contractile substance. This clubbing was found associated with conspicuous nuclear proliferation. From the club-shaped ends of the old fibers proceeded budlike processes each one of which contained a nucleus or group of nuclei. The development of these buds, according to a procedure similar to that we have described above for the muscle spindle cells, they considered the common method of restoration of the tissue. They could not be certain whether a new fiber developed from each process or whether two or more buds might fuse to form a single fiber. The essential point in this process appears to us to be the fact that the contractile substance of the new fiber had its origin in the old fiber sarcoplasm, and as such represented a simple continuation of this old fiber. It is obvious at once that the method of regeneration described in connection with the muscle spindle cells attributes the origin of the new fiber sarcoplasm to a new and entirely separate element, the newly produced muscle cell, and hence bespeaks a discontinuous mode of regeneration of the fiber as opposed to the continuous process of Neumann and Nauwerck, although the two processes are fundamentally the same, so far as the muscle cell originates from the substance of the old fiber.

The terminal clubbing of the partially degenerated fibers we have frequently met with in our sections. The development of these forms from the old fiber with their resulting production of mononuclear muscle cells and syncytial masses of muscle cells is dealt with at length above. It has not been mentioned, however, that the large syncytial masses may sometimes be seen isolated from the old fiber stump. As isolated structures they are well preserved and actively growing, as one may judge by the presence of mitotic figures in the nuclei. It is suggested that such a collection of isolated sarcoplasm and nuclei may develop into single muscle cells according to the plan which has just been described. The syncytial masses do not necessarily appear in a terminal position.

We have thus far tried to show that essentially, in our material, only one method of regeneration is responsible for restoration of the muscle, and that consists of the formation of new muscle cells from old muscle

nuclei and sarcoplasm, and the subsequent development of these muscle cells into muscle fibers. A true continuous budding process has not been observed, although certain microscopic pictures might suggest such an interpretation. A similar conclusion was reached by Volkmann [11] in his study of typhoid muscle changes, although he described both terminal and lateral budding in experimentally produced regeneration in animals.

It is difficult to be sure of the rôle which the sarcolemma plays in the regenerative process. It is certainly preserved in some areas and destroyed in others. Where it remains intact, all the regenerative processes occur within its limits, and it seems to give direction to the newly developing fiber. In places where the sarcolemma does not persist, the new fiber is restricted in its growth by the surrounding normal fibers or, in their absence, by the endomysium.

Of the origin of a new sarcolemma, we are able to say nothing. The cases which furnished our material were all fatal, most of them terminating before sufficient time had elapsed for the complete restoration of the muscle. The later stages of regeneration are not shown in our material.

Everything in these cases points toward a complete restoration of the degenerated muscle provided the process be not interrupted as, however, happened in all. The absence of any scar formation or even fibroblastic proliferation after from fifteen to twenty days of disease is striking, especially when compared with the extraordinary changes in the muscle itself. This is in marked contrast to the condition as seen in experimental degeneration and regeneration when the muscle defect is replaced by a large fibrous scar only toward the edges of which can regenerative changes be found. It is also in striking contrast to the scar formation in the healing of all muscle wounds, even when the element of infection is absent.

It has already been noted that during the process of degeneration the blood vessels and nerves seem to remain unaffected, just as in the degenerative phase during regeneration the nerves and vessels do not appear to be concerned. It is obvious, however, that the nerve endings in their relation to the newly formed muscle must be affected. Because of the character of our material, we have been unable to study this very important and interesting phase of the problem. In our experiments, satisfactory regeneration (always partial) has not been obtained to permit of detailed study. It can be stated, however, that regeneration as well as degeneration proceeds entirely independent of the nerve supply. This was shown by Kirby,[18] who severed all nerves to a selected muscle and then produced the characteristic changes.

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18. Kirby: Experimentelle Untersuchungen über die Regeneration des quergestreiften Muskelgewebes, Beitr. z. path. Anat. u. z. allg. Pathol. **11**:302, 1892.

In going through the literature on regeneration of striated muscle, one finds that there are two widely differing schools of thought, especially among the older writers. The first considered regeneration as a function of the nonmuscular tissue, that is, the cells of the perimysium. Zenker [1] first put forth this idea. He was supported later by Waldeyer [2] and Wittich. The second school was composed of those who believed the old muscle alone to be the source of the newly formed fibers. Those who followed this line of thought fall into two groups, one of which regarded regeneration primarily as a function of the sarcoplasm (i. e., terminal and lateral sarcoplasmic budding) and the other composed of those who regarded the muscle nuclei as the primary source of the new muscle (i. e., development of new fibers from true muscle cells derived from muscle nuclei). Among those who shared the former opinion were Weismann, Neumann [5] and Nauwerck.[13] Peremeschko, Coldberg, Weber,[3] Hoffmann,[4] Kraske [12] and Volkmann [11] were foremost in maintaining the latter view.

So far as we have been able to see, the process of degeneration and regeneration in our fatal cases of pneumonia is in every way similar to that described originally by Zenker and later by Hoffmann and Volkmann in typhoid fever. Our interpretation of the details of the process seems to lead us to the view that regeneration is a function of both muscle nuclei and sarcoplasm, the regeneration being effected through the intermediate formation of muscle cells which develop quite apart from the old fiber and which cannot be interpreted as true bud formations.

SUMMARY

In fatal pneumonia secondary to influenza or measles, degeneration of the rectus abdominis muscle may occur as a complication. Twenty-five such cases are briefly described.

The muscle lesion usually consists of hyaline degeneration of the contractile substance of the fibers, although abscesses may be found. The hyalinization of the muscle may result in rupture with subsequent hemorrhage. Details of the degenerative process are described.

The cause of the muscle degeneration is unknown, although the evidence at hand indicates that a bacterial toxin is responsible. In the characteristic lesion, no evidence is found pointing to a localized infection in the muscle.

The muscle lesion apparently is not dependent on a pneumonia due to any specific type of organism, although the cases under consideration were all due to one of three organisms—pneumococcus, streptococcus and *Bacillus influenzae*.

The degree of muscle degeneration is not dependent on the duration of the pulmonary infection, but rather parallels the intensity of the infection.

Following degeneration of the muscle, regenerative changes occur which apparently lead to total restoration of the affected muscle. This regenerative process is described in detail, the essentials of which are as follows:

1. The hyaline contractile substance is removed through the activity of mononuclear wandering phagocytic cells which are of extramuscular origin.

2. The sarcolemma may or may not remain intact.

3. The muscle nuclei of the old fiber proliferate and produce new muscle cells, their cytoplasm being derived from the sarcoplasm of the old partially preserved fiber. From these muscle cells the new fiber develops, either from growth of the individual cell or from fusion of several cells.

4. No terminal or lateral bud formation is observed.

5. Regeneration of the destroyed muscle apparently is total. No scar is produced within the affected muscle.

ACUTE MYOCARDIAL SYPHILIS*

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At a meeting of the association of American Physicians in May, 1925, Warthin [1] read a paper in which he described eight cases of sudden death which he attributed to an exacerbation of latent myocardial syphilis. The pathology of these cases was remarkable, for in addition to the usual perivascular collections of lymphocytes and plasma cells with here and there older areas of scarring, there were collections of acute inflammatory cells in the myocardium. In the midst of these collections, numerous spirochetes could be demonstrated. All the patients were men, of young or middle age, and for the most part apparently in good health. Symptoms of cardiac failure developed with great rapidity, and the cases terminated fatally in from a few hours to a few days.

This contribution of Warthin's is a most important one, for, as he remarks, it deals with a form of syphilis of the heart unknown to the textbooks of internal medicine and pathology. The present communication deals with what appears to be another example of the condition, this time in a woman.

REPORT OF A CASE

History.—A woman, aged 62, was sent in from the country to the Winnipeg General Hospital in May, 1923, suffering from weakness, polyuria and polydypsia. The urine contained a considerable quantity of sugar. The systolic blood pressure was 210 mm. Her condition was disclosed as diabetes and essential hypertension. In spite of vigorous insulin treatment, her blood sugar could not be kept below 0.2 Gm. per hundred cubic centimeters. She was sent back to her home in the country, where she continued the insulin treatment under medical supervision. All went well until the middle of August, 1925, when one day she was suddenly seized with a feeling of great faintness, and fell to the ground. She felt that she was going to die, and was bathed in a cold sweat. When the acute attack passed off she was left very weak, and complained of constant pain in the precordial region. She was admitted to the hospital, but rapidly grew worse and died three days later.

Postmortem Examination.—At necropsy, a rich and varied pathology was disclosed. The pancreas was of firm consistence, and the ducts were dilated. The islets of Langerhans showed pronounced hyperplasia. An extreme degree of atheroma was observed in the pancreatic artery and this was true also of the aorta in its entire extent, the renal arteries, the coronary arteries and the vessels

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1. Warthin, A. S.: Sudden Death Due to Exacerbation of Latent Syphilitic Myocarditis, Am. Heart J. **1**:1, 1925.

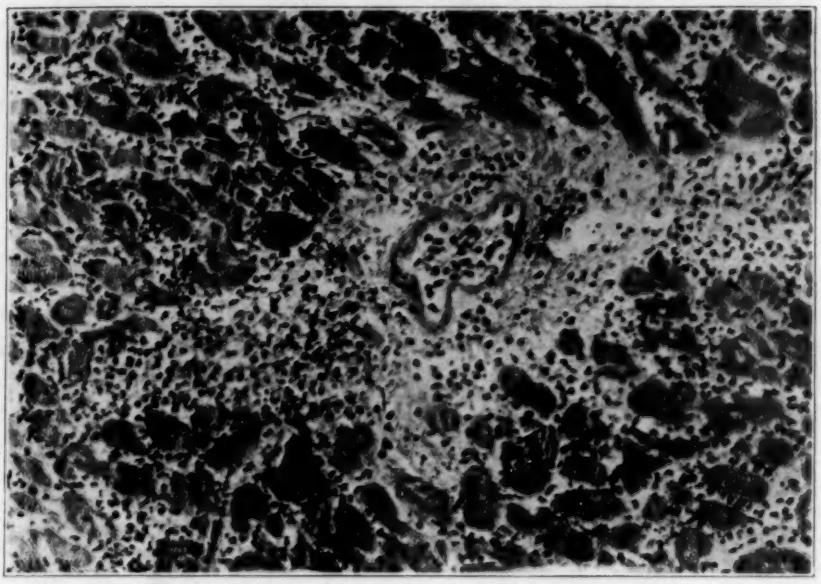

Fig. 1.—Acute syphilitic lesion in the myocardium. The cells are mainly polymorphonuclears; × 350.

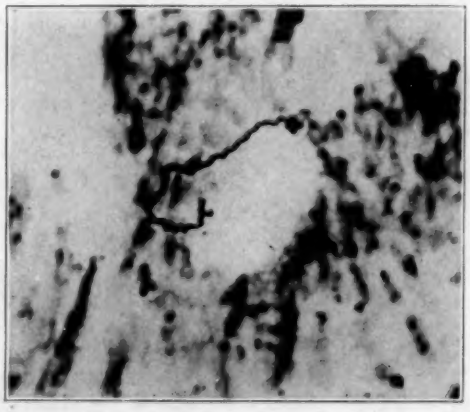

Fig. 2.—Two spirochetes lying end to end and situated in the acute lesion; × 2,200.

at the base of the brain. The kidneys provided an excellent example of the primary arteriosclerotic form of so-called chronic nephritis. Old tuberculous lesions were found at the apex of the right lung.

The heart weighed 300 Gm. The wall of the left ventricle was hypertrophied, measuring 20 mm. in thickness. The valves appeared normal, and no lesions were noticed in the myocardium. Under the microscope, collections of lymphocytes and plasma cells were found here and there in relation to the blood vessels. Similar collections were found in the adventitia of the left coronary artery. In the thoracic aorta the lesions were much smaller. These cellular collections, in conjunction with myocardial scars, led to a diagnosis of latent syphilitic myocarditis and aortitis. In addition to these familiar lesions, peculiar collections of polymorphonuclear leukocytes were found in the interstitial tissue of the wall of the left ventricle (fig. 1).

At the time we were unable to explain the meaning of these collections of acute inflammatory cells. Some months later, however, Warthin's paper appeared with its fine illustrations of similar collections. This led us to a renewed study of our own material. Sections were stained by Warthin's modification of the Levaditi method, and collections of spirochetes were found in the acute inflammatory lesions (fig. 2). It would appear, therefore, that we are justified in regarding this as another example of the interesting condition first described by Warthin.

SUMMARY

A description is given of a further example of the condition known as "sudden death due to exacerbation of latent syphilitic myocarditis."

The patient was a woman, whereas the previous cases have all occurred in males.

MELANO-EPITHELIOMAS OF SWINE

TRANSPLANTATION AND CULTURAL EXPERIMENTS *

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We have observed three cases of spontaneous malignant melanotic tumor in swine. These swine were all of the same breed and of the same herd, and in each case the tumor occurred in the same situation, in the skin of the right flank. Various experiments were performed to determine whether the disease could be reproduced. They consisted in the transplantation of autogenous, homogenous and heterogenous tumor tissue, the inoculation of animals with tumor filtrates, and bacteriologic studies of the original tumors and metastatic lymph nodes. The implantations and filtrate inoculations were made in swine, dogs, rabbits, guinea-pigs and fowl. Cultures of organisms obtained from melanotic tumors were injected into swine, rabbits and guinea-pigs.

REVIEW OF LITERATURE

Melano-epitheliomas form a large percentage of the malignant tumors of certain animals, especially the horse. Lubarsch [1] quotes Folger who reports that 42.82 per cent of 527 cancers found in 175,745 horses were malignant melanomas. As a basis of comparison, Lubarsch further says that in 143,309 dogs examined, there were 865 cancers, only 0.35 per cent of which were melanotic neoplasms. In 18,113 cadavers examined in Berlin in the thirteen years prior to 1920, 2,274 contained malignant tumors; of these 0.89 per cent were melanotic. Melanosis of hogs has been noted by several observers.[2] The pigment is deposited in the panniculus adiposus, bones, kidneys and liver. Adult animals are most often affected. As an index to the incidence of melanosis in swine, the United States Department of Agriculture, Bureau of Animal Industry, during the fiscal year ending June 30, 1924,

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* From the Section on Surgical Pathology, Mayo Clinic, and the Division of Experimental Surgery and Pathology, the Mayo Foundation.

1. Lubarsch, Otto: Zur vergleichenden Pathologie der melanotischen Gewächse, Med. Klin. **1**:195-199, 1920.

2. Merillat, L. A.: The Principles of Veterinary Surgery, ed. 2, Chicago, Alex. Eger, 1916.

inspected 54,416,481 swine. Of this large number only 161, or less than three in 1,000,000, were condemned on account of melanosis.[3]

There is confusion in veterinary literature as regards the terms melanosis, melanoma, melanosarcoma and melano-epithelioma, these names apparently being used synonomously. On account of this error, few accurate data are available regarding the incidence of malignant melanotic tumors in cattle, sheep, goats and hogs. Melanosis, abnormal pigmentation of the skin, is common in most domestic animals. In 1806, Laennec [4] regarded melanotic tumors as a variety of cancer. Trousseau and Leblanc [5] concurred in this opinion. In 1813, Gohier [6] noted the frequency of this type of tumor in white horses.

The observations regarding the incidence of melanoma in the horse are perhaps the most accurate. Gray and white horses are most commonly affected, although these tumors have been found in horses of all colors. Van Dorssen [7] found that 44.87 per cent of 234 gray horses had malignant melanomas. The age was an important factor in the development of these tumors in gray horses, as they appeared at about the time that the hair changed from gray to white. The relation of age to incidence of the tumors is illustrated in the tabulation.

The Factor of Age in the Development of Melanomas in the Horse[7]

Age, Years	Horses	Tumors
6	17	..
6 to 8	45	5
8 to 10	52	19
10 to 12	90	37
12 to 14	38	27
14 to 15	7	5
15	15	12

Breed and sex are of no apparent etiologic significance with regard to melanoma in the horse. Gohier [6] reported his observations on a white stallion which indicated an apparent hereditary influence in the etiology of melanoma. This animal was used for breeding for a few years, then developed melanosis and was no longer serviceable. All of his progeny inherited his coat and developed melanoma in adult life. Even those born while their sire was still a colt and before he developed the disease were not exempt.

3. United States Department of Agriculture, Bureau of Animal Industry, personal communication.

4. Laennec: Sur les mélanôses, Bull. Fac. de méd. de Paris **1**:24-26, 1812.

5. Trousseau and Leblanc: De la mélanose, Arch. gén. de méd. **17**:165-188, 1828.

6. Gohier, J. B.: Mémoires et observations sur la chirurgie et la médecine vétérinaires; ouvrage couronné en grande partie par la Société d'agriculture du départment de la Seine, Lyon **16**, 1813.

7. Van Dorssen, quoted by Lubarsch.

There is a wide variation in the degree of malignancy of melanoma in horses. Gray horses frequently have melanotic tumors which are comparatively benign. The region of the tail and perineum is the most common site of malignant melanotic tumors in the horse.

Broders and MacCarty,[8] Dawson,[9] and others, have described the appearance of malignant melanotic tumors in man. Horwitz[10] has recently reviewed the literature, especially that bearing on the production of pigment.

EXPERIMENTAL STUDY

The swine which were the subject of this study were all pure-bred Duroc hogs, one female and two males. The animals were all about 6 weeks of age when the tumors were first noted. At this time no wart, mole or nevus could be demonstrated at the site of the lesion. The nodules were raised, black, hard and flat,

Fig. 1.—The original tumor and the adjacent, enlarged prefemoral lymph node of one of the swine.

about 2 cm. in diameter (fig. 1). The testicles of the males (nos. 1 and 2) were excised, and during the following six weeks these animals grew at the same rate as the rest of the herd. In one (swine 2) the tumor remained stationary in size, while in the other (swine 1), it grew so large that it dragged on the ground and interfered with walking. The female (no. 3), on the contrary, lost weight, and the tumor at the flank doubled in size in six weeks.

The swine were anesthetized with ether and the tumors excised. Subcutaneous autogenous transplantations were made in one of the males in the region of the nipples through sterile trocars and in the flank through a stab wound. Homogenous transplantations were made in like manner in three swine of the same herd. Heterogenous transplantations were made in dogs, guinea-pigs, rabbits and fowls through trocar and stab wound. A filtate of the original tumors from one of the swine was prepared according to the method described by Rouss.[11] The

8. Broders, A. C., and MacCarty, W. C.: Melano-epithelioma: A Report of Seventy Cases, Surg. Gynec. & Obst. **23**:28-32, 1916.

9. Dawson, J. W.: The Melanomata: Their Morphology and Histogenesis, Edinburgh M. J. **32**:501-732, 1925.

10. Horwitz, Alec: Nonmelanotic Melano-Epitheliomas and Their Relation to Melano-Epitheliomas, unpublished.

11. Rous, Peyton: A Sarcoma of the Fowl Transmissible by an Agent Separable from the Tumor Cells, J. Exper. Med. **13**:397-411, 1911.

tissue was ground up in a sterile mortar with sterile sand, suspended in Ringer's solution, and filtered through ordinary filter paper. Amounts varying from 1 to 3 cc. were injected subcutaneously into animals of the different species mentioned. Cultures were made of the original tumor and of the metastatic tumors in lymph nodes. The tumor tissue was ground in a mortar with sterile salt solution and inoculations made into two culture tubes, each of dextrose brain broth, pancreatic digest broth, meat infusion broth and soft agar mediums. One of each of these tubes was overlaid with sterile liquid paraffin to obtain partial anaerobiosis. The organisms found in these cultures were injected subcutaneously into swine and intravenously into rabbits.

Histologically, the tumors were much alike and of approximately the same grade of malignancy. The most striking characteristic of these tumors was their large content of melanin (fig. 2). In some places this element was so concentrated that it absolutely blotted out all other struc-

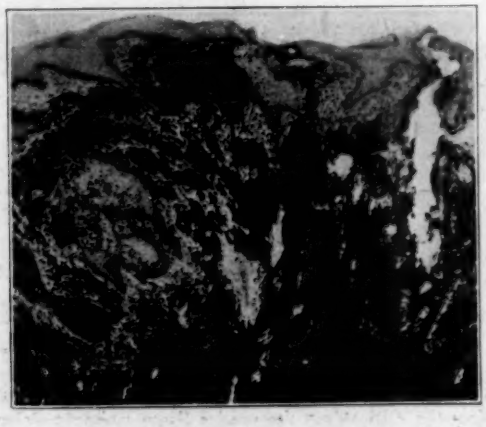

Fig. 2.—Section of an original melanotic neoplasm illustrating the various types of cells and the large amount of melanin present; × 30.

tures. Round, oval and spindle-shaped cells were found in the sections. Some areas of the tumors were composed almost entirely of round and oval cells in an irregular, ill defined, alveolar arrangement, whereas other areas consisted almost purely of spindle-shaped cells. The pigment was intracellular and extracellular, as has been noted by Kaufmann,[12] Lubarsch,[1] Broders and MacCarty,[8] and Dawson.[9] In these tumors the fibrous connective-tissue cells were usually heavily pigmented, although there were marked exceptions which we have already noted. Histologic study of the original tumors of the skin revealed the apparent origin of the malignant cells from the basal layer of the epidermis (fig. 2). Sections from metastatic nodules contained the same type of

12. Kaufmann, Eduard: Lehrbuch der speziellen pathologischen Anatomie, Berlin, W. deGruyter & Company **2**, 1922.

cells as the original tumors, but generally speaking the pigmentation was not so intense. In the involved lymph nodes the malignant cells were first seen in the channels just beneath the capsule, and later they invaded the substance of the gland.

RESULTS

One male (swine 1) weighed 35 Kg., and the tumor after excision weighed 1.6 Kg. The prefemoral lymph nodes on the right side were involved, and these were removed with the original growth. The animal suffered no apparent ill effects from the extirpation. At postmortem examination six months later no metastatic growths were found, and no recurrence was grossly visible at the site of the previous operation. In the other male (swine 2) there was no involvement of the prefemoral lymph nodes when the original tumor was removed. Following this

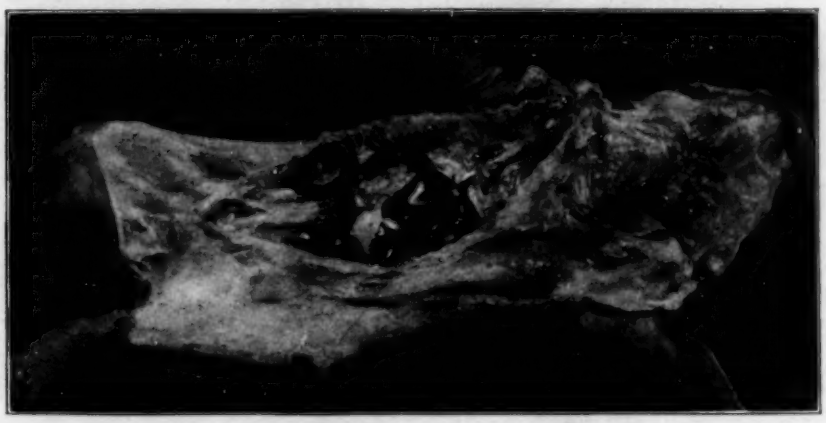

Fig. 3 (swine 3).—Metastatic melanomas in the lymph nodes, kidneys, lungs and liver.

operation the animal continued to grow and remained apparently healthy, but black pigmentation of the skin appeared adjacent to the scar. A biopsy of the indurated portion of the scar four months after removal of the original tumor revealed a recurrence of the malignant neoplasm. This hog continued to grow and remained well. After eight months' observation, he weighed about 95 Kg. At necropsy gross and microscopic recurrence of the melanoma was noted in the scar of the previous operation and also metastatic involvement of the right prefemoral lymph nodes. No other pathologic changes were found. The female (swine 3), because of her moribund condition, was chloroformed, and necropsy was performed the day after removal of the original tumor. There was widespread metastasis of the melanoma involving the prefemoral, periaortic, abdominal, axillary and cervical lymph nodes, as well as the lungs, liver and kidneys (figs. 3, 4 and 5). The largest metastatic growth was about 5 cm. in its greatest dimension.

None of the autogenous and homogenous transplants developed into tumors. The implanted tumor bits were palpable for a few weeks, then gradually disappeared. Biopsy at the site of inception of tumor tissue five and six months after implantation revealed only melanin. One of the swine with homogenous transplants was observed for nine months.

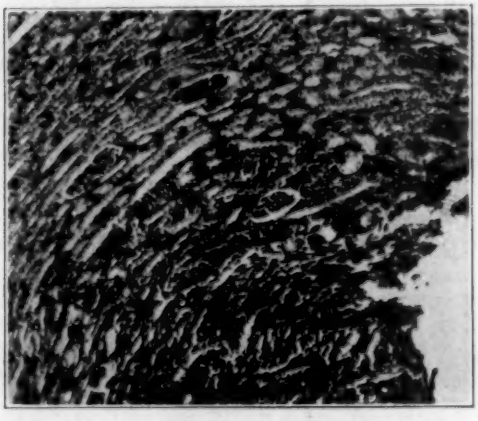

Fig. 4.—Section of a malignant melanotic neoplasm of the kidney which is apparently invading and pushing to one side the renal parenchyma; × 60.

Fig. 5.—Metastatic melanotic nodule in the liver, revealing the wide variety of cells making up the tumor as well as the irregular distribution of pigment. The amount of pigment in this section is much less than that in figure 2; × 100.

At necropsy melanin was found at each implantation site. The pigment was in the subcutaneous fat and fascia, the aponeurosis of the muscles, intermuscular connective tissue and wandering cells. The heterogenous transplants were likewise unsuccessful. However, in one guinea-pig the implanted tissue increased in size for one month until it was 8 mm. in diameter, and appeared to have been successful in producing a new

growth. The animal was anesthetized and half of the nodule removed. This was divided into three parts; two portions were implanted subcutaneously into other guinea-pigs and the third was fixed for histologic section. Microscopic study of this tissue revealed a few endothelial leukocytes, lymphocytes and foreign body giant cells, and large quantities of melanin, but no tumor cells. Following biopsy the tumor in the donor guinea-pig immediately regressed. The transplanted bits disappeared within fourteen days. Postmortem examination, eight months later, of the donor guinea-pig revealed a deposit of melanin at the site of the implant. Microscopic study revealed melanin in the subcutaneous fat, in connective tissue cells, plasma cells and between the muscle bundles. In a chicken the transplanted tumor bit formed a small nodule which was visible and easily palpable after five months. A biopsy was performed at this time, and microscopic examination revealed melanin in the subcutaneous tissue surrounded by lymphocytes but no malignant cells. This fowl came to necropsy eight months after the transplantation of tumor tissue. Deposits of melanin were grossly visible at the site of implantation. Microscopic examination revealed that the melanin was completely surrounded by lymphocytes, and in places germ centers had developed.

From 1 to 3 cc. of the filtrate was injected subcutaneously into swine, rabbits, a chicken, a dog and guinea-pigs. The pigment diffused into the subcutaneous tissue, and in the white skinned animals was visible for from six to eight weeks, but no tumors developed after eight months. When this filtrate injection was combined with transplantation of bits of tumor tissue, the nodules opposite the site of implantation were present and palpable for from two to three weeks longer than when tissue transplants alone were made.

Cultures of the original tumor from the right flank revealed *Bacillus welchii*, a staphylococcus and a gram-positive diplococcus. No attempt was made to separate these organisms. Five cubic centimeters of a two day old culture was injected subcutaneously into a hog. Seven days later, 8 cc. of an original culture was injected in the same location, the right flank. A nodular abscess with multiple discharging sinuses formed at the site of inoculation, but this later disappeared. Cultures were made from prefemoral metastatic growths removed at necropsy, and a gram-positive diplococcus was obtained in pure culture. This organism resembled that described by Minette.[13] From 2 to 6 cc. of a three day old culture was injected intravenously into rabbits, causing no apparent change in the animals.

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13. Minette, E. P.: Pathogenicity of the Organisms Isolated from Nonulcerating Cancerous Growths, Proc. Roy. Soc. Med., Path. Sect. **7**:36-48, 1914.

COMMENT

Goujon [14] produced melanosis by implanting bits of melanotic tumors from patients in dogs. Merillat [2] quotes Bayer, who stated that melanosis could be transferred from the horse to the dog. Virchow [15] was unable to produce malignant melanoma in dogs and rabbits by transplantation. We have produced melanosis of the tissues at the site of implantation in all species used, but never a true melanotic tumor.

Although the number of animals studied is small, some suggestive observations were made. In the female swine widespread metastasis developed, whereas in the males metastasis did not extend beyond the adjacent lymph nodes; this suggests the possible influence of castration on the growth and spread of the tumors. Histologically the melanomas closely resembled each other, and all were of about the same grade of malignancy. Cori,[16] Loeb,[17] and Woglom [18] have observed the influence of castration on the development and growth of malignant tumors. The fact that orchidectomy preceded autogenous transplantation and that this method of experiment was used only in castrated animals may aid in explaining the negative results obtained. Another factor which may have influenced the negative results in the experiments with homogenous transplants was the high differentiation or marked pigmentation of the tumors. In some sections of the melanomas only a thin rim of cells at the margin was apparently actively growing. The remainder of the tumor cells and interspaces was packed with melanin and probably not very active. Histologic study of the transplanted tumor bits revealed great numbers of lymphocytes surrounding the implanted tissue. These observations coincide with those of Loeb [19] and Murphy and Morton [20] regarding the influence of lymphocytes on the fate of transplanted tissue.

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14. Goujon, E.: Inoculation de matière mélanique, Compt. rend. Soc. de biol. **4**:93-98, 1869.

15. Virchow, quoted by Merillat.

16. Cori, C. F.: Discussion, J. Cancer Res. **9**:501-502, 1925.

17. Loeb, Leo: Further Investigations on the Origin of Tumors in Mice. VI Internal Secretion as a Factor in the Origin of Tumors, J. Med. Res. **40**:477-496, 1919.

18. Woglom, W. H.: Immunity to Transplantable Neoplasms, Proc. Second Pan-American Scient. Cong. **10**:362-366, 1915-1916.

19. Loeb, Leo: The Analysis of Factors Which Determine the Life and Growth of Transplanted Tissues, Proc. Soc. Exper. Biol. Med. **18**:153-155, 1920-1921. Loeb, Leo, and Leopold, Samuel: On the Difference in Results Obtained After Inoculation of Tumors Into the Individual in Which the Tumor Had Developed Spontaneously, and Into Other Individuals of the Same Species, J. Med. Res. **17**:299-319, 1907-1908.

20. Murphy, J. B., and Morton, J. J.: The Lymphocytes in Natural and Induced Resistance to Transplantable Cancer. II. Studies in Lymphoid Activity, J. Exper. Med. **22**:204-211, 1915.

The experiments with filtrate injections suggest that this kind of malignant tumor of swine cannot be produced by a filtrate agent.

A possible hereditary influence in the malignant melanomas of swine is suggested by the occurrence of the tumors in closely related animals and their development in the same region of the body.[21]

The bacteriologic investigations, although negative, are too meager for the formation of definite conclusions.

SUMMARY

Malignant melanotic tumors were observed in three young swine of the same herd. This variety of malignant tumor is rare in swine. The transplantation of tumor tissue, and the inoculation of swine, dogs, rabbits, guinea-pigs and fowl, with tumor filtrates and cultures were not successful in reproducing the malignant disease, although melanin was constantly found at the site of implantation of tumor bits. Castration of the donors and recipients used in the experiments with homogenous and autogenous transplants may have been a factor in the negative results.

21. Slye, Maud: Experimental Studies in Heredity, Proc. Second Pan-American Scient. Cong. **10**:354-360, 1915-1916.

CORTICAL HETEROTOPIA IN THE PONTILE MENINGES

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Heterotopias of the gray matter into the white matter of the spinal cord undoubtedly occur, although many of those reported in earlier years were probably due to imperfect technical procedures. Somewhat more common are cortical heterotopias into the subcortical white matter and into the walls of the ventricles. These occur with considerable frequency in tuberous sclerosis, of which I have reported a case.[1] The heterotopia of cerebral cortex found in the following case was an incidental finding at necropsy, and I have found no reference to a similar case.

REPORT OF A CASE

A colored woman, aged 55, developed an acute toxic psychosis, and within a few days after her admission to the hospital died of lobar pneumonia. Over the upper end of the pons on the right side (fig. 1) was a small flattened oval mass of soft consistency and pearly pink, circumscribed, lying wholly in the meninges and connected with the pons only by pial tissue. This mass resembled normal cerebral cortex in every way, was not invading, and had no connection with any nerves.

Microscopically it was easy to recognize cerebral cortex (fig. 2). Beneath a delicate fibrous glia layer containing many myelin bodies was a broad molecular layer with tangential nerve fibers and normal vessels. Below this layer little tendency to cortical lamination was recognizable, but there was aggregation of fully developed neurons into small groups that greatly resembled the cyto-architecture of the hippocampal gyrus. The upper portion of the cortex contained medium sized pyramidal cells whose apical dendrites pointed in various directions. There were aberrant cells of smaller size in the lamina molecularis. Individual cells were well developed, but the cytoplasm showed some tendency to granularity and vacuolization and contained a small amount of lipoid pigment. Nerve fibers were rather few and took the stain poorly. Most of them ran tangentially, although some ran perpendicularly; but there was no aimlessness about their course, and as far as they could be followed, they ran in straight lines. Only rarely did a myelin sheath appear. Glia cells were normal in number and development.

This cortical heterotopia was connected with the pons by rather fibrous meninges that showed areas of cellular hyperplasia. Two distinct sets of meninges were recognizable, however, one for the pons and one for the heterotopia. A delicate meningeal film covered the heterotopia externally, but this part of the mass was unfortunately damaged during preparation.

There were no other malformations of the brain, and both macroscopically and microscopically it showed only moderate degenerative changes probably of toxic origin, and slight hyperplasia of the vascular endothelium.

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1. Freeman, Walter: Tuberous Sclerosis, Arch. Neurol. & Psychiat. **8**:614 (Dec.) 1922.

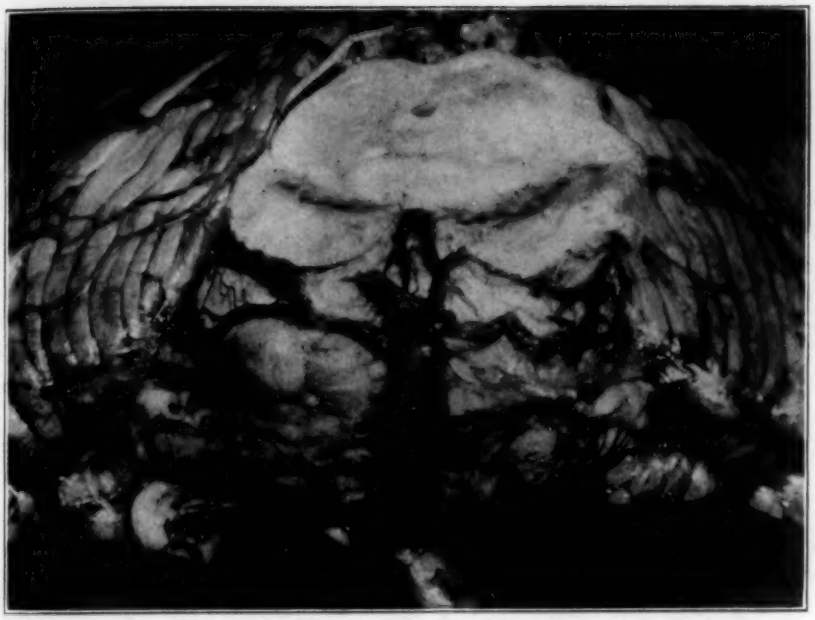

Fig. 1.—Pons and cerebellum showing small mass embedded in the meninges.

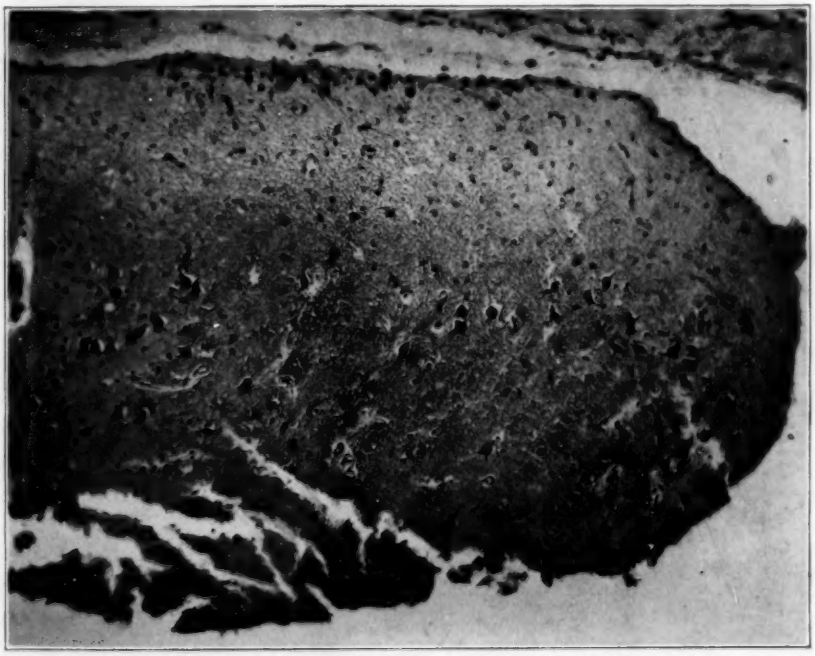

Fig. 2.—Microscopic section of mass showing broad molecular layer above with groups of medium sized pyramidal cells resembling the cortex of the hippocampal convolution.

This heterotopia, then, clearly consists of cerebral cortex in an extraordinary location. The arrangement of cells in small groups like those found in the hippocampal convolution suggests its derivation from this region. The mechanism of its snaring off and implantation into the pontile meninges is obscure. Its development and differentiation are remarkable considering that it is wholly autonomous, unconnected by nerve fibers with the main body of the central nervous system.

LIVE FISHES IMPACTED IN FOOD AND AIR PASSAGES OF MAN

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The medical bibliographies, under the heading "Foreign Bodies," contain pages of references to such bodies which have become lodged in the throat, esophagus and air passages of human beings. If these had been correctly titled, I am sure that many of them would be found to refer to animate as well as inanimate bodies, to living organisms. In fact, one not infrequently reads in medical literature, and even occasionally hears in daily life, of the swallowing by persons drinking from springs or brooks of worms, leeches, *Crustacea* and even small amphibians. But that live fishes ever become ingested is certainly a new thing and by most of my readers unheard of and probably not believed. Yet it is true, and the object of this article is to bring together from widely separated and obscure sources the accounts of this phenomenon. When the reader has perused the article, let him make up his own mind as to its credibility.

My attention was called to this curious and interesting subject by a short note in *Science,* Dec. 5, 1924, by the dean of American ichthyologists, Dr. David Starr Jordan. In this he presents the following data, which it seems advisable to give in full in his own words since the quotation will serve to set forth the essential facts of this rather widely alleged phenomenon.

> I have received from Mr. Nisuke Takahasi, a teacher in a high school in Kumamoto, Japan, a specimen of a fish somewhat noted in Japanese surgery.
>
> It is a fish two and four-fifth inches (7.0 cm.) long taken from a man's throat, in which it had become lodged. The specimen concerned is a common fresh water fish of the clear streams of southern Japan, locally known as *Oyarami* or *Kawamebaru,* very closely related in fact as well as in appearance to some of our American fresh water sun-fishes (Centrarchidae). Its scientific name is *Bryttosus kawamebari* (Schlegel).
>
> The specimen is virtually perfect, although apparently somewhat emaciated. How it was swallowed is not explained, but it is evident that its sharp dorsal spines would hold it in place once swallowed. The specimen was presented to Stanford University by Dr. Toyoji Nishiyama, of the Municipal Hospital at Kuverme, at the suggestion of Dr. Chiyomatsu Ishikawa, of the Imperial University of Tokyo.

A copy was made of Jordan's note, and this was laid aside. During the winter of 1923-1924 the whole forty-two volumes of the catalog of the Surgeon General's Library were checked for articles on fish for the

continuation card catalog of our "Bibliography of Fishes," and from them a number of fish-in-the-throat articles were noted. Later, during the summer of 1925, a fortunate chance brought to my attention Gould and Pyle's most interesting work "Anomalies and Curiosities of Medicine" (Philadelphia, 1897), and from it other references were taken. These titles were worked up and others added in the library of the New York Academy of Medicine during the fall of 1925 with the efficient help of Mr. Frank Place, assistant librarian. Everything has been looked up and checked, and it is believed that all known accounts are included herein.

THE OLDEST ACCOUNT

A chance reference to an account in "Wanley's Wonders" led me to the first edition (1678) in the New York Public Library, and from it I extracted the following interesting incident:

> A certain Priest that was well skill'd in swimming and groping for Fish, had in a deep place, under the Banks, light * of a Pearch, which to hold the better, he put into his mouth, and so to swim back to his companions; the Pearch, with her strugling, slipt so far into his Throat, that the miserable Priest was strangled by it, notwithstanding all the endeavours his associates could use to the contrary; *sic perca fuit* (saith my Author) thus the fish was his fate.

The "Author" quoted is referred to as "Zuin. Theat," volume II, lib. 7, p. 515. Nonplussed, I referred this to Mr. H. M. Lydenberg, reference librarian of the New York Public Library, who readily answered that the full reference is to Theodore Zuinger's "Theatri Vitae Humanae," Basiliae, 1571. Reference to Zuinger's huge folios in the library of Columbia University showed volume II to be lacking, but while idly turning the pages of volume XVII, my eye was caught by the centered heading "Pisce," and here was my citation in sixteenth century Latin. However, it was not original, but in turn is quoted from "Gilb. Cogn. Narrat. 1, I." Here again Mr. Lydenberg cleared up this title as Gilbert Cognatus (Latin form of Cousin), "Narrationum Sylva," etc., Basiliae, 1567. This work is found in the United States only in the Widener Library of Harvard University, whence it was courteously sent to me as an interlibrary loan. In it is found the original Latin, of which Wanley's English version is a good translation. It reads as follows, the earliest published account (1567), (with a possible earlier edition, Lyons, 1548) of a fish impacted in the throat:

> Quidam sacrificus piscandi & natandi peritissimus, quum manu in quodam profundo gurgite parcam cepisset, oriq; mordicus inseruisset ut ad sodales enataret: Parca in gulam elapsa miserum sacrificulum in manibus sodalium nihil non tentantium exanimavit.

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* Light of = chance upon, meet with, discover. Compare Sedley's "Altamira," 1687, IV, i, "If I light of him, I will tear his goatish eyes out."

In order to bring like accounts together, the data herein presented will be collected under the headings: mouth, pharynx (or throat), esophagus; and larynx, trachea, and bronchi (the latter three considered as one). Many of the accounts say "throat," by which, as best one can make them out, pharynx is meant.

IMPACTION IN THE MOUTH

There is one well determined case of a live fish impacted in the mouth, but before setting it out in detail it may be of interest to quote here from Roosevelt's "Through the Brazilian Wilderness" (New York, 1914, p. 52), an incident which approached the matter in hand. He writes of the fierce and voracious fishes called perais or piranhas that "One man . . . having his hands full, tried to hold one fish by putting its head in his mouth; it was a piranha and seemingly stunned, but in a moment it recovered and bit a big section out of his tongue. Such a hemorrhage followed that his life was saved with the utmost difficulty." The fish was presumably of some size, otherwise it would probably have gone down his throat, with fatal results.

Dantra (1878), a surgeon of troops in British Indo-China, reports an interesting case of a trooper with a live fish in his mouth. Here is his description of the phenomenon which took place on the journey between Rangoon and Tounghoo, Burma. He writes:

> A few days ago . . . I was called upon to see a private who . . . was dying from suffocation. I hurried . . . to the patient, and . . . found the man in a fearful state of agony, with a live fish (some 3 inches in length and one in breadth at its widest part) lying on the dorsum of the tongue. His mouth was full of bloody clots, and the Hospital Assistant was trying to pull the fish out of his mouth with an ordinary dressing forceps. The result of this operation was that the forceps, having a very feeble hold over the fish, brought away a few scales only, and the fish remained fixed to its hold. In the act of pulling the scales and fins used to get expanded and thus interfered materially with the extraction. Lest the fish, which was living, should either go down the larynx or pharynx, I caught hold of it with the forceps and then examined the mouth with a view of ascertaining to what part of the mouth it was attached. I found that the fish had caught hold of the man's uvula near the median raphe on the patient's left side. The free margin of the uvula, having the palato-glossus muscle in it, was firmly held in the fish's mouth.
>
> On a moment's reflection, I saw that the pulling operation was unsuccessful, and therefore instead of persevering in it, as the dresser did, I immediately caught the fish's tail with my left hand, and, with my right grasping its head in an ordinary dressing forceps, I used as much lateral pressure on its mouth as possible. The fish, its mouth being violently pressed from side to side, relaxed its hold in an instant and then I had no difficulty in completely withdrawing it.
>
> It lived for some time after its extraction. There was very little subsequent hemorrhage. The uvula was bitten but not torn. The bleeding before extraction was more from the parts in the neighborhood which were injured by the expanded

fins than from the uvula itself. His mouth was then rinsed with cold water, and alum gargle subsequently used. For a couple of days after the accident he could not take any solid food without experiencing . . . pain, but after that he felt quite well, and could take his meals as usual.

On questioning the patient how the accident occurred, I was told that while he was swimming with his mouth open, the fish went in, and in an instant he felt something biting in his mouth. The water in the river where he was swimming being very shallow, he soon got up on his legs, and on examining his mouth, he found the fish stuck in the position above described. He tried to pull it out, but did not succeed. He said it hurt him and so in great fright, holding the fish firmly in his hand, he rushed to the Hospital Boat which was close by.

LIVE FISHES IMPACTED IN THE PHARYNX (THROAT)

The man whose case is related in the preceding paragraph got off lightly; not so, however, the unfortunates in whom the fish passed down into the pharynx. The accounts given from Jordan and from Cognatus say "throat" and the context in each leads to the belief that pharynx is meant.

The earliest strictly medical report of the number of cases to be set forth under this heading is presented by a Dr. Eitner of Steinau in Germany (1850). A man, aged 48, of large stature and strong constitution, who was given to drinking, was the victim. One day when in his cups, he scolded his wife because she had brought to the house for his meal some very small fish. Boastfully declaring that "One does not need first to cook such small trifles, one can swallow them just as they are," he followed words with action and successfully swallowed a small living whitefish. Emboldened by his success and anxious further to show his powers, he took another fish, unfortunately a small perch this time, and essayed to treat it as he had the former. However, this fish was too large to penetrate further than the pharynx. Here it set out its fin rays and stuck fast. This rather large object, by the pressure it exerted, both cut off breathing and interfered with the circulation of the blood in the neck, so that in half an hour the man died before medical aid could reach him.

Our next reference takes us to India where, as we shall see, troubles with fishes impacted in the food and air passages are by no means uncommon. Dr. P. M. White comments (1859) on the frequency of such occurrences in the Indias, makes suggestions as to the handling of these extraordinary happenings, and gives the following interesting personal experience at Rangoon, Burma, in 1855:

I was requested by Dr. Davidson, Senior Surgeon, Madras Army, to attend him in a consultation upon an Hospital Bheestee (Pecoully), who had a fish jump into his mouth while bathing, and which had stuck in his throat. Dr. Dale, Bengal Service, was my guest at the time, and we repaired together to this to me novel case. The man was well built and very muscular, as most Madras

servants are, and respiration which had nearly ceased was entirely through the nose. On opening the mouth the tail of a large catfish presented itself, with the body firmly fixed within the fauces, and filling up the isthmus completely. It had entered flat, so that the fin of one side was posterior to the velum pendulum palate, and opened out on any attempt being made to withdraw the fish. Dr. Davidson had made several fruitless efforts to remove it, but it could not be made to pass onwards into the oesophagus and it was impossible with such strong sharp fins to draw it forward.

Before my arrival, Dr. Davidson had decided upon opening the oesophagus in the neck, and drawing the fish head foremost through the external opening; the operation had been commenced but abandoned. What was to be done, the man could not be allowed to die thus, and every moment threatened to be his last. The case being now left to me, I determined upon completing the oesophagotomy commenced by Dr. Davidson. Having steered clear of various vessels and nerves, and satisfied myself of the whereabouts of the inferior thyroid and the recurrent laryngeal, I was compelled by the earnest entreaties of my two friends, from proceeding further with the operation, and the wound was accordingly closed for the second time. That matters could not remain as they were was too evident, so seizing a piece of cane that was lying on the bench, I made it into a strong probang, and with it carefully but firmly endeavoured to pass the fish downwards into the oesophagus. By steady pressure for a few seconds the foreign body moved onwards, but only to complete the catastrophe for the poor fellow at once ceased to breathe, gave one convulsive struggle, and died to all appearances. Nothing now remained but to open the trachea, which was at once done, and respiration being speedily established, the pulse rose and the patient was taken to bed to live or die in peace. *In the course of the night the patient coughed up the fish.* The wounds healed kindly, and the poor Bheestee soon forgot his sufferings, not so the three surgeons. The [joints of the] bones of the fins had become soft by decomposition, and the effort of coughing displaced the fish.

It seems well just here to consider other Indian cases before turning to other countries. Dr. Matthew, an assistant surgeon in the Indian civil service, describes the next case (1872). It seems that on being called up at midnight he found lying on his veranda a man in a comatose condition, covered with cold perspiration, with his teeth firmly clenched, with a barely perceptible pulse, breathing stertorously and with the greatest difficulty. The history of his case is set out as follows:

He was hand-fishing in a bheel, and having captured a fish, he placed it in his basket, from which it escaped into the mud, and having recaptured the fish, he put it between his teeth, intending to bite through its neck and so kill it; while in the act of biting, the fish made its way into his mouth, and before the unfortunate man could seize it with his fingers, had passed beyond reach, and was at that moment stuck in his throat.

On making an examination, I could plainly see the bifid tail of the fish pointing upwards. I was barely able to touch it with my forefinger. It had been dead some hours and emitted a most offensive odour.

In the meantime the poor patient was rapidly sinking, his attempts to breathe were becoming very feeble, and the pulse at the wrist had ceased to beat. The accident had occurred about 12 o'clock in the day, and he had been brought a

distance of nearly 20 miles, and how he had survived so long seemed truly wonderful.

Having wrapped a little lint round the blades of a forceps and having fastened it securely to a piece of whale bone, I passed it downwards, and having satisfied myself as accurately as circumstances would permit that the fish was between the blades of the forceps, I pushed down the clamp and attempted to draw it directly upwards.

This I found impracticable for reasons to be detailed further on. I then began to move it gently from side to side, and after a little time, being, however, obliged to use considerable force, I succeeded in removing the fish entire.

Fortunately for the poor patient, he was quite insensible. Otherwise the agony would have been unsupportable, as the back of the pharynx, soft palate and uvula were much lacerated, a considerable portion of the latter being entirely torn away. All this damage was caused by a formidable dorsal fin armed with numerous sharp points passing in a direction upwards and backwards in the tissues of the back of the throat, rendering the removal of the fish a matter of no small difficulty.

It was about two inches and a half in length, and about one inch in breadth. It is very common in the bheels and muddy tanks. Indeed, its appearance is so well known that it is unnecessary to describe it; suffice to say that it is known as the "koiee-mâch," and I believe to zoologists as the "*Anabas scandens* or climbing tench [perch]."

The patient remained in a precarious condition for some little time; he was subsequently removed to the hospital, and in a few days returned to his home convalescent.

Matthew had no personal experience of other like cases, but his assistant (presumably a Hindu) told him of a relation of his who when a mere child was nearly choked to death in similar fashion. The fish in this case was removed in primitive fashion, vi et armis, by the use of a pair of blacksmith's pincers or tongs.

The following account was presented by a Hindu sub-assistant surgeon who communicated it as a sequel to Matthew's case just set forth. At first I thought that it was the very case referred to in the preceding paragraph, but as it occurred on Jan. 18, 1874, it is of course another one. Mitter (1874), the operator in question, writes that:

About 11 a. m. in the forenoon of the 18th inst. [Jany., 1874], a man came running to the dispensary with a little boy about 5 years old, and stated that the boy, while playing about where some live fishes (*Kholesa mâch*) were kept, happened to put the head of one into his mouth, which made its way into his throat, about two hours previously.

On examination, I found the child was breathing with great difficulty and groaning; pulse rather feeble. On opening his mouth widely and depressing his tongue, I could only see the tail of the fish, but at this stage the child became restless, and I was obliged to stop the proceedings. To put him under the influence of chloroform I thought would be dangerous. I ordered his head to be caught firmly, and his jaws widely separated with a cork; then with a strong pair of forceps I secured the fish between its blades, but found it was firmly caught in the throat; and if I were to make any forcible attempt to drag it out, not only all the soft and delicate parts would be lacerated, but portions would come away

and the result would likely be fatal. I therefore commenced to shake it in the way a man tries to separate a thorny plant entangled in his clothes, and at the same time dragging it gently upwards; in about ten minutes' time I succeeded in bringing the fish out. It was 3½ inches long and 1¼ inches broad and was quite dead.

There was slight bleeding, but on washing the mouth and throat freely with cold water it stopped, and he breathed with ease. By using astringent gargles and warm fomentations externally the boy is doing well.

Mitter states that his fish is named *Kholesa* (*Colisa?*) *mâch* in the Bengali, and that it is very like Matthew's *Koiee* (*Coii*) *mâch*, especially in having a dorsal fin provided with sharp spines directed upward and backward, which makes its extraction very difficult. Examination of Francis Day's "Fishes of India" (1878) shows that the *Coiee mâch* (*mâch* presumably meaning fish) is *Anabas scandens*, and the *Kholesa* (or *Colisa*) fish is *Trichogaster*. These fishes are kindred genera belonging to the family *Labyrinthici*—fishes provided with accessory breathing organs which enable them to live a considerable time out of water.

The next account is an anonymous one published as a subsection—"Fish in the Throat"—of "Letters from Madras" in the *London Medical Times and Gazette* for the same year (1874) as the preceding. It reads as follows:

One morning, in the midst of the visit [to the clinic of Dr. George Smith and Dr. Paul], word was brought to Dr. Paul that a man had come to the hospital with a live fish in his throat. Accordingly there was a general move to the verandah, where we saw a coolie, aged about twenty, walking in, supported by a man on either side, breathing with intense difficulty, and in great distress. The story was soon told. He was that morning employed in emptying a tank and in catching the fish that were left floundering when the water was drawn off. In his eagerness he had one under each foot, one in each hand, and to make sure of a fifth, he tried to secure one by taking its head between his front teeth; but the fish was too quick for him, and wriggling itself free from the teeth, made its way into the pharynx. A fish of the same sort and size was produced; it was like a perch, about four inches long, with a most formidable dorsal fin, the spines of which, when erected by being pushed the wrong way, stood out at least an inch.

A finger passed into the throat easily felt the fish. Here was a very pretty case!—but as the first point was to enable the man to breathe, in less time than it takes me to write it, a bed was brought out into the verandah, and he was laid upon it and tracheotomised. Then what was to be done? Pull the fish out! anyone would say; but although it was easy to seize the tail, there were the erect spines of the fins, which would have lacerated the parts past recovery had the fruitless attempt been made. Then it was suggested to push the fish down the throat into the stomach; but alas! it lay doubled up with the head to the left, and this could not be done. Then, when this was ascertained, it was hoped that the head might be turned upwards with a blunt hook, and so be dragged out. But the fish would not move. So it was necessary to leave the patient for a few hours—he was breathing freely, and nourished with beef-tea enemata.

Next morning it was found that the fish had become decomposed, and was easily broken up into a putrid pulp, some of which made its way into the trachea [oesophagus ?], while the spines offered the greatest obstacle to any removal by the mouth. In order to afford room for clearing the throat, the wound made in tracheotomy was enlarged upwards through the junction of the alae of the thyroid; but the patient was very exhausted and died before relief could be given.

I believe this accident is pretty well known amongst fishing communities and that there is a preparation in one of the Scottish universities showing a pharynx with the fish impacted. A short time afterwards, the history of just such a case was related in the Indian newspapers as having occurred in Ceylon. It is said that the fish was allowed to putrefy in the pharynx, whence it was ejected piecemeal next day, and that the patient recovered. But in order that such a policy may be successful the patient must be provided with means of breathing and the fish should have no spines.

Leaving India for the time being we now turn to Europe for accounts of live fishes impacted in the throat, and our first account comes from Toulon, southern France. The case was reported in 1863 by Dr. Arlaud, who thought it a unique one. It seems that on the afternoon of March 19, 1863, a convict, a vigorous man, had fallen to the deck of a hulk in the harbor, had struggled a while, and had become insensible. When Arlaud reached him he found "the lips purplish, the conjunctiva turgid, the veins of the face and neck distended with blood. He had the outward appearance of man just dead of asphyxia." Investigation brought out the facts from one of the warders that the man had been fishing from the coal hulk on which he was found, that he had caught a fish and that after taking this from the hook he had put it still alive in his mouth while rebaiting the hook, that it had penetrated into his throat, and that after some efforts to vomit it up, the poor fellow had fallen down and died.

This recital was received with incredulity by Dr. Arlaud and his assistants and with astonishment by the bystanders. However, the man's jaws were pried open and a finger inserted into his pharynx found a strange body and was pricked by it. A pair of forceps being inserted and firmly set on the body brought to light the tail of a fish. A second and stronger pull with the forceps (the man being dead) brought out a fish 19 cm. (7.6 in.) long by 6 cm. (2.4 in.) in depth, and 3 cm. (1.2 in.) in thickness. The fish was so long that its head had reached to the back of the throat but was too large to penetrate further. Here its fins and scales had so caught in the walls of the pharynx like the "beards" on a "head" of rye, that it held fast and could not be regurgitated. And finally the head, pressing on the epiglottis, had cut off the air supply and had quickly asphyxiated the unfortunate man.

This incident is also referred to by Cobbold (1863) who quotes a clipping from a London paper in which the fish is called a mullet

(Arlaud gave its colloquial French name as *saron*) and is alleged to have penetrated into the gullet. However, as we have seen from the original account, it was found in the pharynx, and had it penetrated the esophagus it could never have been extracted in the manner in which it was.

One published recital of an abnormal incident almost invariably brings out others, and so Arlaud's account evokes an even more interesting one from Dr. Tarneau, who goes more carefully into details than any one yet quoted. We will let him tell the story in his own words:

> On June 16, 1858, the cadaver of a Maltese, of 40 or 45 years and of athletic figure, was laid out in the amphitheater of the medical hospital at Bône (Algeria). Here in a few words is the singular medical history of this man. He was selling fish in the market when a silly woman remarked that his soles were not of premier freshness. At this reproach, badly founded as it appeared, our man too touchy on this point and feeling keenly piqued, cried out in vehement fashion and desiring to prove that his merchandise left nothing to be desired, laid hands on a malacopterygian fish, introduced it into his mouth and bit it with vivacity. The active animal then, being held by the Maltese's mouth ready for swallowing, either in surprise or voluntarily precipitated itself towards the pharynx, helped along by the natural and rapid movements of deglutition.
>
> He immediately called for help, demanded a glass of *eau-de-vie*, became purplish red, his eyes started from their orbits, the veins of his neck swelled, he tottered, fell, struggled and died some instants later.
>
> Desirous of knowing the exact mechanism by which there had been produced such a bizarre death, which had excited to such high degree the astonishment of everyone, I resolved to examine the cadaver in great detail, with the help of one of my good comrades, Dr. Hamel. This was the day following the accident.
>
> The external appearance was that of a man dead of suffocation. The cadaveric rigidity did not allow us to see very far down into the pharynx but we sawed apart the symphysis of the chin, and after having dissected out the different muscular layers in the subhyoid region, we discovered in the lower part of the pharynx the caudal extremity of a sole.
>
> Persevering in our researches, we perceived that the anterior extremity was solidly fastened in the oesophageal opening.
>
> Next we remarked that the dorsal and anal fins, which as everyone knows extend from the mouth continuously to the tail, were twisted like a horn. The epiglottis was lifted up and the belly of the fish was applied to the epiglottic orifice which it hermetically sealed.

This solé was 19 cm. (7.6 in.) long and 7 cm. (2.8 in.) wide, and hence was too large to go down the esophagus. The three unique points about this case are that the fish was doubled up from right to left, i. e., along the long diameter (the length), and that it caught and held the uplifted epiglottis and sealed tight the opening, causing asphyxiation essentially as in Arlaud's case.

Later in the same year (1863), in the same journal, and moved thereto by the two preceding accounts, Dr. Duplouy published a case exhumed from the notes of his confrère, Dr. Phélippeaux. The incident to be noted occurred at Gorée, Senegal, where Dr. Phélippeaux was

in charge of medical affairs in 1851. He was, unfortunately, prevented from making a necropsy by the religious scruples of the people. He tells us that:

> There is taken on the line on the coast of Africa [in Senegal] during winter a delicate fish that is vulgarly called by the name of *crocro,* without doubt because of the peculiar cry or grunt which it makes. This fish, once taken and disengaged from the hook, the blacks have the habit of killing by crushing the head with the teeth. Thus it was that in living up to this practice a young negro of about 12 years fell as though struck by lightning in the midst of his comrades. A *crocro* of small size (about 7 or 8 cm. in length), escaping from a stroke of this use of the teeth and perhaps also because of preoccupation on the part of the fisherman, had introduced itself into the pharynx, where it had penetrated so deeply that one could perceive no more than the end of the caudal fin.
>
> Notified in all haste, M. Phélippeaux arrived a few moments after the accident, but only to find a dead body on which he was interdicted from making any investigation whatever.

IMPACTION OF LIVE FISHES IN THE ESOPHAGUS

As has been seen, when a live fish has penetrated the mouth of a man, it will almost invariably pass on into the pharynx. If large, the fish will be caught here; but if small, the tendency will be for it to pass over the epiglottis and down into the esophagus. The latter type of case will now be presented. The first account seems to have been written by P. D. Anthoniez in *Ceylon Miscellany,* volume 1, no. 2, whence it was transferred to the *Lancet* in 1854, and from the latter journal I have extracted it as follows:

> Singho Naide, a native of Colombo, aged forty, a fisherman by occupation, was taken into the Pettah Hospital on the evening of the 12th of August, 1853, a fish which he held between his teeth while baiting a hook, having slipped back into, and remained impacted in, the oesophagus. . . . On examining the neck, it appeared swollen, with a feeling as if there were fluid in the cellular tissue about the muscles of the neck. In the fauces the tail of the fish was felt, and could be seen distinctly on depressing the tongue. The tail was inclined toward the left side of the throat, showing the direction the fish had taken in its course down the oesophagus. Careful examination externally failed in discovering the situation of the fish, and it was found impracticable to withdraw it from the throat for reasons which will appear obvious when the fish is described. . . .
>
> An incision was made between the exterior edge of the sterno-mastoid muscle and the trachea . . . extending down to the sternum. . . . After a most diligent search both by myself and my friends, nothing was discovered to indicate the spot where the gullet should be divided. The next step of the operation was conducted with great care. . . . The passing of a male catheter was intrusted to Dr. Elliott, who, with no little difficulty, introduced it into the gullet, directed by his fingers, and turned the convex side of it towards the wound. This enabled the part to be seized with a pair of forceps, and a small opening to be made into the oesophagus. The finger introduced into this opening gave the feeling of something cartilaginous being lodged, which was soon found to be the edge of the fish. A polypus forceps was introduced and attempts were made to

extract it, but to no purpose, as the head of the fish was too smooth to be grasped by a polished instrument. A little manoeuvering with the index finger, soon dislodged the fish, which made its exit through the wound, head foremost. . . . The fish was four and one half inches long from head to tail, and one inch and a half broad. It is named by Mr. Gray in his "Illustrations of Indian Zoology," *Anabas spinosus*, and has large and sharp fins, both on the back and near the gills. . . . About a week after the operation, a little nourishment was given through the mouth, but as some of it flowed out through the wound, it was deemed prudent not to repeat the attempt, but to continue nutriment through the rectum. In three or four days more the man was able to take nourishment by the mouth, from which time he began to gain flesh and strength. The wound healed gradually, and he was discharged quite cured on the 23rd of September, with merely a line of cicatrix on the side of the neck. . . . The performance of the operation occupied more than an hour and was done by lamplight.

This incident is referred to by Sir Emerson Tennent in his "Natural History of Ceylon" (1861, p. 251, footnote). He says further that: "Strange accidents have more than once occurred at Ceylon arising from the habit of the native anglers; who, having neither baskets nor pockets in which to place what they catch, will seize a fish in their teeth whilst putting fresh bait on their hook."

In his article previously referred to, published in 1863, Cobbold says that:

In the Anatomical Museum of Edinburgh University there is a solefish preserved (eight inches long and two and a half broad) which, many years ago, caused the death of a fisherman. . . . The man was in a boat drawing a net, and, having his hands engaged, seized the fish by his teeth to prevent its escape through the meshes. A sudden convulsive effort carried the animal down his throat, and, after death, the head was found within an inch of the cardiac orifice of the stomach. The man died from suffocation before the boat gained the shore.

The next account, by Dr. Stewart, comes (like another already given) from Burma, and is the most extraordinary of any as yet presented. Incidentally, it shows the enormous digestive powers possessed by the stomach in some men. Stewart writes from Rangoon (1869) that:

On the morning of the 8th of May, 1869, a native puckally of the regiment, named Chengamully, was brought to the hospital . . . in a state of great distress—suffering from intense pain low down in the oesophagus. There was much difficulty in breathing, and the patient was unable to swallow liquids or solids. He assumed a posture leaning forward, as the attempt to stand erect caused more distress. The patient stated, as also his friends who accompanied him, that on the previous evening, while fishing at "the Lake," he caught a fish, which proved unusually lively, and, in order to extract the hook from its gills, he seized the fish with the fingers of the left hand and the hook with the right, and, with the head of the fish between his teeth, effected his object. He had scarcely done so, however, when the animal, with its long, sharp, dorsal fin, pricked the palm of his hand, causing him suddenly to let go his hold, and involuntarily to open

his mouth at the same time, when the fish bolted down his throat; and although he grasped it by the tail in its descent and squeezed his pharynx with the other hand, all his efforts were ineffectual—the fish made its way to the position above described.

A live specimen of the kind of fish impacted had been brought to the hospital by the man's friends for inspection. It was about the same size, and caught the same evening. It appeared to be identical with the *Anabas scandens* (the walking perch of Ceylon), called by the Hindustanees here the *sooma*. . . . The fish was in length about four to five inches, an inch thick at the shoulder, and in depth about one inch and a half, including a dorsal fin, as sharp as a knife standing up full one-half inch. The attempt to extract the animal with forceps, if such had been at hand, would have failed, and in all probability would have caused serious injury, owing to the sharp dorsal fin, which, when erected to its full extent, inclines towards the tail of the animal; the pectoral fins also inclining in the same direction. It was, therefore, decided to use the probang as the only alternative, and if possible push the animal into the stomach. Owing to the pain and spasm induced, a first attempt failed. On a second attempt the fish was dislodged, and I passed the probang fairly into the stomach with but slight obstruction to the instrument. The patient shortly afterwards left the hospital, able to walk without the assistance of his friends, and relieved of all his distressing symptoms, and, beyond some pain on deglutition for some days afterwards, has since experienced no inconvenience.

Even more remarkable (particularly in the length of time that the fish remained in the esophagus) is the account now to be quoted. It is from the pen of Dr. MacLaren and was written at Iloilo, Philippine Islands, April 23, 1873. Of particular interest to medical men is the account of the treatment made use of in this case.

Simeon ———, a native servant, while fishing in the shallow waters of the rice fields, attempted to kill with his teeth a fish that he had caught, and at the same time groping with his left hand to catch another. The fish, which was about three inches long and one and one-half wide in its broadest part, and having very sharp dorsal and anal fins, escaped down his throat. The fish, called by the Spaniards "martynico," and by the Indians "poyo," is a species of perch, probably [certainly] the *Anabas;* for its habits, as described by the natives, correspond with those ascribed to the *Anabas*—viz., its power of travelling a considerable distance over land and from one fresh-water pond to another, and the great time it can live out of water.

When I saw the patient at 1 a. m. on February 25th, and five hours after the accident happened, I found him sitting up in bed, suffering greatly from difficulty in respiration, making violent efforts at vomiting, and bringing up quantities of blood and mucus. The face, neck and chest were greatly swollen from emphysema. I passed a probang, and found the fish to be low down in the oesophagus, but could move it only very slightly, while from the direction of the rays of the fins it was impossible to extract it. Further attempts to push the fish into the stomach causing great distress, I determined on not interfering more until the following day, and ordered small quantities of vinegar-and-water to be taken frequently and also small doses of morphia to allay spasmodic action.

Feb. 25th, 10 a. m.: The emphysematous condition has increased; but the patient can swallow small quantities of beef-tea. The fish is still firmly impacted.

26th: After taking vinegar-and-water this morning at 6 a. m. he vomited up a considerable portion of the fins, and I succeeded in pushing the fish into the stomach with a probang. The empsysema has extended to the scrotum. Ordered the following mixture: Nitric acid, two drachms; tincture hyoscyamus, three drachms; glycerine, one ounce; water to six ounces: 1 tablespoonful every three hours. Diet to consist of milk and arrowroot.

27th: Great pain in throat; other symptoms the same. Ordered one ounce of castor oil.

28th: The oil has acted well, the first evacuation containing dark blood, the others natural. There is still great pain in the throat, and expectoration of semipurulent mucus. Hot poultices to be applied over the throat.

March 1st: Great pain over larynx and trachea; the voice almost gone. To continue the poultices and to have an expectorant mixture.

3rd: The voice greatly improved and emphysema diminishing. From this date recovery took place rapidly, and on March 10th he was able to resume his ordinary work.

There is one last account, this from Gould and Pyle (Anomalies and Curiosities of Medicine, 1897, p. 569). It is not original with them, but as they give no reference, the best I can do is to say so and quote the excerpt as follows:

There is an interesting account of a native of India, who, while fishing in a stream, caught a flat, eel-like fish from fifteen to sixteen inches long. After the fashion of his fellows he attempted to kill the eel by biting off its head; in the attempt the fish slipped into his gullet, and owing to its sharp fins could not be withdrawn. The man died one hour later in the greatest agony; so firm was the eel impacted that even after death it could not be extracted, and the man was buried with it protruding from his mouth.

LIVE FISHES IMPACTED IN THE AIR PASSAGES LARYNX, TRACHEA AND BRONCHI

It would seem that so large and bulky an object as even a small fish could not penetrate the human larynx, one of the most sensitive and best protected organs in the body, covered over as it is by the epiglottis whose marvelous reflex activity results in its instantaneous closing down when touched ever so lightly by anything other than the column of air, and over which all solid objects glide to pass into the esophagus. Furthermore, one can hardly understand how a fish, granting that it is under the epiglottis, could pass down through the constricted space between the vocal cords. However, that such have penetrated the larynx, trachea, and even into the upper part of the bronchi we shall now see. Furthermore, the trachea is so short (4 to 4.5 inches in a man) that a fish of ordinary small size in it would have its head at the forking of the bronchi and its tail in the larynx; hence all three of these organs will be treated as one in considering fish impacted in the air passages.

The first reference to a fish in the trachea is the oldest known medical citation to this phenomenon, and is antedated only by Cognatus' brief note (1567) as the earliest reference to a fish impacted in the mouth or adjacent openings. This later account is from the pen of a French physician, Gautier, and is dated 1785. The place was the parish of Brétignolle, Poitou, Biscay coast. A prosperous farmer there with his servants went to the sea to fish, and, following the bad habit of the coastal inhabitants of this and other regions in taking small fishes in their teeth, lost his life. Gautier remarks that few years go by without such accidents taking place. His account is as follows:

> With the sixth try of the net he caught a small fish, which he put between his teeth in order to hold it better. The fish freed itself, and slid precipitately into the tracheal passage before the farmer could catch it with his hands. The efforts the man made to get out the fish were useless. His servants noticed the agitation of their master and when his gestures explained the cause, one of them put a hand into his mouth and felt with the end of his finger the tail of the fish, which he tried in vain to draw out. During this time, some of the employees . . . had carried the dying man to Marais-Girard, a village fully a quarter league distant from the place where the accident had occurred. There they made him swallow two or three spoonfuls of brandy. This caused great efforts without any relief. When I arrived I found the sick man without pulse, without movement, cold, and expiring; I could only detect some faint convulsive movements of the muscles of the larynx.
>
> To make sure of the nature of the foreign body, I put the index finger of my left hand into his mouth, which I held open with a small bit of wood between his clenched teeth. I encountered the tail of a fish which stuck up three or four lines above the epiglottis toward the mouth. I tried to extract the animal with pincers, but could only get out a piece nine or ten lines long, which seemed to me to be from a *loche de mer,* and which I showed to ten or twelve spectators. As the sick man was dying in spite of my attempts, I made him take two grains of an emetic in an ounce of warm water, which I put into the back of his mouth with a spoon. This did not succeed any better. I did not see anything to do except to make a bronchotomy which I proposed even although the patient seemed to have expired, for he seemed to me to be in a more favorable state than that of a drowned person. The people would not consent to this operation. The poor creature died less than two hours after his accident and about ten minutes after my arrival. Nevertheless I did not desert him until I had made numerous attempts. I had a helper raise the glottis so as to turn the foreign body if it were possible and make it easier to get with the pincers. I passed my finger around and even behind the glottis to make sure where the fish was, and I found it stuck precisely in the tracheal passage.

Our next account is dated 1842 and is from the pen of a Dr. Rémy. The incident took place near Epernay in the department of Marne, and hence the fish was a fresh-water species. It seems that a man named Drury (23 years old) had made a wager that he could swallow a small fish. This, however, instead of passing down the esophagus and into

the stomach, passed through the larynx into the upper part of the trachea. Dr. Rémy was sent for and tells that:

> On my reaching the sick man, one hour after the accident, I found him lying on his back, his head raised, and a prey to all the symptoms of beginning asphyxia. An oesophageal sound which I passed down one of his nostrils (his jaws were violently contracted), and which I was able to push clear to the cardiac orifice of the stomach, thoroughly convinced me that the foreign body was not in the oesophagus: but that it was in the lower part of the trachea, as I readily proved by percussion, auscultation and symptoms which were construed from these. Death was imminent; only one resource remained—the operation of tracheotomy. This I proposed, but met with most strenuous opposition on the part of the family, the persons who surrounded the moribund party, and singularly enough on the part of a confrère, Dr. P., called in by me to aid me with his counsel. I exhausted all the means of persuasion in my power, I brought forward all the most plausible reasons, but all in vain—asphyxia was completed an hour after my arrival.

Here again death was due to the obstinacy and ignorance of the friends and relatives of the sufferer. However, Dr. Rémy obtained from the mayor of the commune an order to perform a necropsy (violently opposed by the family), and, to show that tracheotomy might have saved the man's life, he performed this operation with all the care he would have used on the living man. This he describes briefly and concludes:

> As soon as the cut was laid open, so that my hand introduced into the opening felt the tail of the fish below the wound, I made the situation clear to my confrère and to the various persons standing round, and then I proceeded to extract the fish. This part of the operation offered some small difficulties. The little fish was of the kind called *perchette* and was 7 cm. (2.8 in.) long and 2 cm. (0.8 in.) in depth.

Our remaining accounts take us to Italy, where the same practice noted in the immediately preceding paragraphs is in vogue, and the same results follow.

In 1879, Dr. Teresino-Attilio Prati of Spezia gave a long and detailed account of a suffocation due to a fish in the trachea and right bronchus. Too long to be quoted in full, the essential facts will now be culled and set forth. His vivid account is in part as follows:

> A youth of 18 years with two companions was amusing himself by fishing along the shore of the Gulf of Spezia. There is among fishermen here the custom of crushing between the teeth the head of the fish as soon as it is caught in order to kill it. This unfortunate youth [following the custom] was about to close his two rows of teeth on a fish when it slipped from his careless hand and penetrating his mouth, forced itself past the epiglottis, went through the trachea, and stuck in the right bronchus from which it could not be removed. The unfortunate youth was at once taken to the *Ospedale Civile* and when the staff was summoned they marvelled when they heard that he had swallowed (so his

two companions said) a living fish, not remembering either to have heard or read of a similar case. But the story of his two companions left no doubt that a fish had penetrated either into the oesophagus or trachea. . . . Here was a well-built muscular youth of eighteen threshing about and fighting death like a drowning man, and so strongly that three nurses and two policemen were barely able to prevent him from doing himself injury. He gave forth groans like one suffocating, uttered words in smothered, scarcely intelligible tones, indicated with his hand on his chest that he felt his breathing being cut off, and declared that he had therein a fish (locally called *Linguata*) of the length of his index finger. This he indicated with his hand and was confirmed by his two companions. Like a condemned man, he begged for help, at one instant falling back on his bed in a moment of calm, and in the next beginning again his agonizing sounds. His respiration was very fast and irregular, and it was impossible to put one's ear to his chest for even a moment. His efforts to cough were followed by an enormous swelling of the neck and face.

In a very short time I tried all the most common methods of relief, even introducing a flexible rod tipped with a sponge into the oesophagus and down to the stomach without encountering any obstacle. This and the administering of antimony tartrate were for the purpose of bringing about vomiting, but neither in the least eased the sufferings of the poor boy. Further I sought to cause an attack of coughing both by tickling the glottis with my finger and with a little sponge, but all in vain.

In the meantime Prati had summoned two colleagues, and the matter of a tracheotomy was fully discussed. His probang experiment showed conclusively that the esophagus was clear, hence the fish was certainly in the trachea and possibly at the forking of the bronchi. Tracheotomy was decided on and performed, but so tightly was the fish wedged in the air passage that it could not be extracted, and after about and hour and a quarter [after entering the hospital?] the poor boy died.

Necropsy was performed the next day, and, since the subject's people were violently opposed to this, it was confined merely to the removal of the trachea and bronchi. But the sternum was raised sufficiently to see that all thoracic organs were much congested and that the right lung was highly inflated with imprisoned air, which escaped with considerable force when the right bronchus was cut. Dissection of the removed trachea and bronchi showed the fish at the point of bifurcation with about its anterior two-fifths in the right bronchus and the remainder in the trachea, where the tail was so bent as to form an incomplete valve to the opening of the left bronchus, partially cutting off the air supply to the left lung.

The fish was readily recognized as that colloquially called *Linguata* (tongue fish) or *Sogliola* (sole), and scientifically known as *Solea vulgaris*, the common sole. It was 11 cm. (4.4 in.) long, 3 cm. (1.2 in.) deep, and 1 cm. or 0.4 in. thick—so large that every one was surprised that it could have penetrated to the bifurcation of the trachea.

The remainder of the article is given to a lengthy discussion of the accident and to a consideration of whether or not an operation should have been performed. However, Prati adds two interesting but non-attested accounts of fishes in the air passages. One is of a Neapolitan fisherman whose relatives related the story of his death by suffocation due to a fish. The other story was related by one of the hospital attendants and is to the same effect.

On reading Prati's article, Dr. Giovanni Cardo Tempesti wrote him a letter describing a similar case in his own practice at Livorno and discussing at some length the question of an operation. This letter Prati had published in the same journal (*Lo Sperimentale*) in which his own appeared. Tempesti's account reads:

> It concerns as usual a robust fisherman, an adult, who, in order to detach a small fish tangled in the net, so his companions tell, tried to crush its head with his teeth. The fish slipped into his throat and the man fell dead in a few seconds, not leaving time to get medical aid. The necropsy made by dexterous examiners showed that the murderous fish was a sole, of the species vulgarly called *linguattola*, the length, so my recorders tell me, of four thumbs [inches] including the short tail; or about 11 centimeters [4.4 inches] as in your account. This fish occupied the larynx with the anterior third of its body; the remainder was free and the tail rested on the base of the tongue in such a way that it would have been easy to catch hold of it if a surgeon had been on the spot. I do not know, though, whether even if convenient to grasp, one could have pulled it out of that narrow place because of the imbrication which is acute, formed of the swimming spines which are along the margin [in the dorsal and anal fins] of this fish otherwise without scales; but one cannot ignore this possibility supposing that the resistance of the spines—when the force applied to the extraction was the usual one—was greater than that pulling strength.

These interesting accounts of Prati and Tempesti were abstracted in the *Gazette Hébdomadaire des Sciences Médicales*, Montpellier, Feb. 1, 1880, and in them the colloquial Italian names "linguata" and "linguattola" were used. Furthermore, both authors say the offending organism was a fish, both call it the sole, and Prati specifically identifies it as *Solea vulgaris*. Notwithstanding all this, the French translator (who was wise enough to write himself down as anonymous) discusses learnedly and at length as to the specific identity of the linguattola which he writes linguatule. Then having set up this straw beast, he proceeds to discuss the zoologic position of the linguatule, quoting some five pages of authorities and finally deciding that it is an arthropod. He finds that there is such an animal parasite, and that it parasitizes domestic animals and even man himself. He finds, further, that the linguatule is found as a parasite in the nasal cavities of man. From that point on his attempted explanation is of course easy.

On reading the article referred to, an Italian doctor named Sampolo, professor of natural history in the municipal school at Dolbert, sent to

the editor of the journal in which the former article was published, a letter which effectually disposes of the whole matter. From it I quote as follows:

> In spite of the learned dissertation of your collaborator, it is impossible to admit in the two cases reported by M. M. Prati and Tempesti that the matter deals with the helminth called linguatule: the offenders in this double homicide were really, according to my opinion, two fishes. In many parts of Italy the pleuronectid fish which we call sole, is called *lingua;* and as in both cases the fish could only have been of very small size, the two Italian doctors employed a diminutive of the word lingua, linguatolla, which the translator of the Journal de Montpellier boldly renders as linguatule.

SUMMARY

The data given show that on the coasts of France and Italy and in India and the Far East, fishermen are accustomed to take live fishes between their teeth either to kill them by biting, or to hold them while the hands are used to free the hook or net. A fish so held, if it pricks the man's mouth with its spines or sets up any sudden movement, will readily cause the involuntary opening of the mouth with a resultant entrance of the fish into the throat of the man.

In time, accounts of the impaction of live fishes in the food and air passages range from Cognatus, 1567, to Jordan, 1924—a range of 357 years; or counting strictly scientific references, from Gautier, 1785, to Jordan, 1924—a range of 139 years.

Twelve countries are represented in these various accounts as follows: India leads with five cases, and France follows with three; Burma and Italy tie for third place with two cases each; Algeria, Ceylon, Germany, Japan, Philippine Islands, Scotland and Senegal are credited with one each; and finally there is one account (Cognatus', the oldest) not assignable to any country.

With reference to the fishes which bring about the troubles described, our data are more or less indefinite so far as concerns giving the fish its scientific name. The exception seems to be that in four cases (from India, Ceylon, Burma and the Philippine Islands) the culprit is pretty well identified as *Anabas scandens,* the climbing perch. Four cases each are assignable indefinitely to perches and soles—except that one perch from Japan bears the name *Bryttosus kawamebari* since it fell into the hands of an ichthyologist, and that the Italian soles were presumably *Solea vulgaris.* Then there is a catfish from Burma convicted of the offense of entering the pharynx. Another fish (from India) seems pretty sure to be a *Trichogaster* and fairly closely akin to *Anabas;* and, finally, the remaining six are so imperfectly described or else designated by such trivial local names as to be unidentifiable.

On inquiring as to the numbers of fishes found impacted in the various organs, the facts show up as one would expect *a priori*. One would suppose that if a fish got into the mouth it would go further. And we find but one lone case in which the fish remained in the mouth. This seems to be due to the fact that as soon as it entered (Dantra) the frenzied man at once laid hold of its tail and the equally scared fish expanded its fins and gill covers and laid hold of the man's uvula with its mouth.

One would expect that the larger number would go into the pharynx where most of them would be detained, and this we find in ten out of twenty cases. Of the nine remaining cases, five fishes were small enough or active enough, or else the esophagus in every case was large enough, to allow the fish to penetrate that organ. As indicated previously, it would seem quite impossible for even small fishes to get underneath the epiglottis, penetrate the small opening between the vocal cords and descend into the trachea. Yet four cases have been recorded in which this has happened—and in one of these the fish partially penetrated the right bronchus.

Lastly, reference must be made to the treatment employed in each set of cases. This must of course vary with the degree of penetration that the fish has made. In the one case where the fish stopped in the mouth, removal was comparatively easy—the chief complication arising from the fact that the fish had laid hold of the man's uvula. However, the fish's tail being held in one hand and the head grasped securely with forceps, a gentle rotation from side to side freed the fish, and it was successfully extracted.

But when the fish has penetrated the pharynx, if the isthmus of the fauces is closed, and if the fish is large and spinose, the condition is much more serious, and asphyxiation is likely to occur shortly. Of the ten cases of pharyngeal impaction reported, seven resulted in death either before surgical aid could be procured or in spite of all efforts. In two cases the fish, being grasped firmly, shaken gently and rotated from side to side, relaxed its hold and was removed, with complete recovery by the patient. In two cases tracheotomy enabled the patient to breathe while decomposition at the high temperature of the body reduced the fish to fragments. In one of these cases, about twelve or fifteen hours later the patient coughed up the fragments and recovered. The other patient, treated in like fashion, was unable to throw off the fragments, and died.

Of the five cases of penetration of the esophagus, there were two deaths and three recoveries. In one case in the latter group, esophagotomy and removal of the fish gave the man his life. In another case the fish was pushed with a probang into the stomach, where it was

digested, with complete recovery. In the third case, since the fish could not be either extracted or pushed into the stomach, it was allowed to remain and become macerated; whereupon the patient vomited part, and the remainder passed into the stomach, with complete recovery.

The impaction of a fish in larynx, trachea or bronchus will surely result in death unless a tracheotomy and removal of the offender is effected quickly. Of the four known cases, one patient was dead before the physician arrived. In two cases permission for the operation was ignorantly refused, and death quickly ensued. In the fourth case, the trachea was opened, but the fish was so firmly wedged in the fork of the trachea, with its head in the right bronchus and tail covering valve-fashion the opening of the left bronchus, that it could not be extracted—as was shown by necropsy.

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CARCINOMA

GRADING AND PRACTICAL APPLICATION *

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Cancer is a disease that directly or indirectly interests all mankind; it is no respecter of station, but attacks all races and classes. It even attacks the lower orders of life, from the finest horses and dogs to the contemptible banana fly.

Certain persons think of cancer as something foreign to the body; but it is a strictly domestic affair, because it springs from one's own cells, and, in varying degree, obeys the limitation of growth, as manifested by the fact that some cancers grow slowly and closely imitate normal cells while others grow with extreme rapidity and depart markedly from the structure of normal cells. The high mortality produced by the rapidly growing cancer has caused man to dread the very word cancer, regardless of its high or low lethal capacity. It has become rather well known that the grading of cancer depends on cell differentiation, that process closely related to evolution by which cells advance from an immature to a mature or specialized state or acquire a distinct and separate character. The fertilized human ovum by the process of cell differentiation eventully produces a mature man.

I am quoting from my first paper [1] on the method of grading cancer, as follows:

> The most important factor in squamous-cell epithelioma of the lip seems to be the degree of cellular activity. The cells of some epitheliomas of the lip show a marked tendency to differentiate, that is, to produce a growth similar to the normal; the pearly body is an example. The pearly body corresponds to the horny layer of the epidermis. In other squamous-cell epitheliomas there is no differentiation whatever. In the large majority of growths whose cells show no tendency to differentiate, or at least very little, there are many mitotic figures.
>
> In studying these epitheliomas, therefore, it occurred to me that they should be graded according to differentiation and mitosis, special stress being laid on the former. The grading was made on a basis of 1 to 4, and absolutely independent of the clinical history. If an epithelioma shows a marked tendency to differentiate, that is, if about three-fourths of its structure is differentiated epithelium and one-fourth undifferentiated, it is graded 1; if the differentiated and undifferentiated

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* Read before the Section on Pathology and Physiology at the Seventy-Seventh Annual Session of the American Medical Association, Dallas, Texas, April, 1926.

1. Broders, A. C.: Squamous-Cell Epithelioma of the Lip, J. A. M. A. **74**: 656-664 (March 6) 1920.

epithelium are about equal, it is graded 2; if the undifferentiated epithelium forms about three-fourths and the differentiated about one-fourth of the growth, it is graded 3; if there is no tendency of the cells to differentiate, it is graded 4. Of course, the number of mitotic figures and the number of cells with single large deeply staining nucleoli (one-eyed cells) play an important part in the grading.

In more recent papers,[2] I revised this slightly as follows:

The mitotic figures and the one-eyed cells are undifferentiated cells, and really should be considered only as such; however, when mitotic figures are numerous, especially if they are of an irregular nature, one is inclined to raise the grade to some extent. . . . Instead of a grade 1 epithelioma in which about three-fourths of the cells are differentiated and one-fourth undifferentiated, should be substituted a grade 1 epithelioma, one in which differentiation or self-control ranges from almost 100 to 75 per cent, and undifferentiation from almost nothing to 25 per cent; a grade 2 epithelioma, one in which differentiation or self-control ranges from 75 to 50 per cent, and undifferentiation from 25 to 50 per cent; a grade 3 epithelioma, one in which differentiation or self-control ranges from 50 to 25 per cent, and undifferentiation from 50 to 75 per cent, and a grade 4 epithelioma, one in which differentiation or self-control ranges from 25 per cent to practically nothing, and undifferentiation from 75 to practically 100 per cent. So far as an estimation of the ultimate result is concerned, this revision will have no effect on grades 1 and 2, but will affect slightly grades 3 and 4, because a small percentage of neoplasms, formerly classified grade 3, will now be classified grade 4. In other words, the most malignant of the grade 3 neoplasms will be classified in grade 4.

I[3] have endeavored to point out how a number of carcinomas, by the process of differentiation, put the brakes on themselves, so to speak. Squamous-cell epitheliomas control themselves by differentiating into keratin, which, when found in circumscribed masses, are called pearly bodies, and into cells which, if they do not contain keratin, have differentiated beyond their ability to reproduce, such as the large, flat squamous cells.

Basal-cell epitheliomas control themselves by producing cells similar to the normal basal cells of the skin, and melano-epitheliomas by producing melanin, which is a product of the epithelial cells and indicates an attempt at self-control.

Adenocarcinomas control themselves by differentiating into gland or glandlike structures, sometimes with the production of colloid, mucus, or a mucoid or pseudomucinous material. Primary carcinoma of the liver has been known to produce bile.

It is quite obvious that a carcinoma whose cells increase by geometric progression, without differentiation beyond the point of reproduction, would grow faster and be more malignant than one that caused a number of its cells to differentiate beyond the point of reproduction.

Up to Nov. 1, 1924, after excluding the inoperable cases and those in which death followed operation, data were obtained in 880 cases of graded epithelioma.

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2. Broders, A. C.: Epithelioma of the Genito-Urinary Organs, Ann. Surg. **75**:574-604, 1922; Cancer's Self Control, M. & J. Rec. **121**:133-135, 1925.

3. Broders, A. C.: The Grading of Carcinoma, Minn. Med. **8**:726-730, 1925.

Of the grade 1 group, or cases in which there was from almost 100 to 75 per cent of self-control, a good result was obtained in 90.2 per cent.

Of the grade 2 group, or cases in which there was from 75 to 50 per cent of self-control, a good result was obtained in 62.16 per cent.

Of the grade 3 group, or cases in which there was from 50 to 25 per cent of self-control, a good result was obtained in 24.82 per cent.

Of the grade 4 group, or cases in which there was from 25 per cent to practically no self-control, a good result was obtained in only 10.09 per cent.

Martzloff [4] has divided carcinoma of the cervix uteri into three groups, using the principle of cell differentiation. I have divided epithelioma of the cervix into three grades. In making this gradation I intended to use four grades as in squamous cell epithelioma of the lip, but none of the cases fell into a corresponding grade 1. In comparing the good results in these cases of epithelioma of the cervix with those in Martzloff's series, one is struck with the marked similarity between them; for instance, the 47 per cent of five-year cures in his spinal cell type of carcinoma corresponds to my grade 2, with 53.33 per cent of good results; his transitional type has 24.2 per cent of five-year cures, which corresponds to my grade 3 with 21.56 per cent of good results; his fat, spindle cell type has 9.5 per cent of five-year cures, which corresponds to my grade 4 with 9.52 per cent of good results. The average duration after operation of all three grades of cases was 8.96 years.

Greenough [5] recently divided cancer of the breast into four groups according to cell differentiation, thus: group 1, much differentiation; group 2, moderate differentiation; group 3, slight differentiation; group 4, almost no differentiation (cases highly malignant). In group 1 there were six cases with four cures (66 per cent); in group 2, nineteen cases with nine cures (47 per cent); in group 3, forty-three cases with ten cures (23 per cent); and in group 4, twenty-two cases with no cures.

Greenough's comment on these results is as follows: "These figures appeared so well to justify the correctness of the assumption that the degree of malignancy could be determined by the histological appearance of the original tumor that a more detailed study of the material was made." He further states:

> The disadvantage of recognizing four classes as compared with the relative simplicity of making only three groups was at once apparent, and it was determined to review the material again and reclassify into three groups: high, medium,

4. Martzloff, K. H.: Carcinoma of the Cervix Uteri; a Pathlogical and Clinical Study with Particular Reference to the Relative Malignancy of the Neoplastic Process as Indicated by the Predominant Type of Cancer, Bull. Johns Hopkins Hosp. **34**:141, 184, 1923.

5. Greenough, R. B.: Varying Degrees of Malignancy in Cancer of the Breast, J. Cancer Res. **9**:453-463, 1925.

and low malignancy. This was done again by me without reference to the clinical history or to the first classification, and was repeated by Dr. James Homer Wright.[6] We differed materially on seven cases, but after discussion we were able to eliminate these differences and to come to substantial agreement.

He further divided his three groups into *A* and *C* groups: *A*, those without glandular involvement, and *C* those with glandular involvement. In this reclassification he used seventy-three cases. In group 1, of low malignancy, there were nineteen cases, in eleven of which there was no glandular involvement with nine cures (82 per cent), and eight with glandular involvement and four cures (50 per cent). In group 2, of medium malignancy, there were seven cases without glandular involvement with three cures (43 per cent), and twenty-six with glandular involvement with eight cures (31 per cent). In group 3, of high malignancy, there were five cases without glandular involvement with no cures, and sixteen with glandular involvement and no cures. In group 1 there were 68.5 per cent of cures; in group 2, 33 per cent, while in group 3 there were no cures. Greenough worked his series over from different angles and came to conclusions that are well worth reading.

Turning to the practical side of the grading of cancer, it is well known that cancer of grade 1 shows practically no tendency to metastasize, and therefore in dealing with such neoplasms it does not seem necessary to remove the regional lymph nodes. This saves the patient unnecessary operative procedures. As practically all cancers of grade 4 with metastasis prove fatal sooner or later, the patients should not be subected to an operation involving the regional lymph nodes unless they are in close proximity to the primary growth, cancer of the stomach for example. Judd,[7] New [8] and Figi [9] believe it is useless to perform block dissection of the neck in the presence of a grade 4 epithelioma of the lip, tongue, cheeks, floor of the mouth or antrum, etc. In cases of cancer of grade 2 and in a certain proportion of those of grade 3, with metastasis, removal of the regional lymph nodes offers a permanent cure in a fair number of cases, as evidenced by the fact that ten (33.3 per cent) of thirty patients with squamous cell epithelioma of the lip of grades 2 and 3, with metastasis in one group of submaxillary lymph nodes, were living and well on an average of six and one-fifth years after removal of the nodes.

Braasch,[10] Crenshaw [11] and Bumpus [12] use fulguration in practically all of their cases of grade 1 epithelioma of the urinary bladder, and in a

6. Wright, J. H., quoted by Greenough, footnote 5.
7. Judd, E. S.: Personal communication.
8. New, G. B.: Personal communication.
9. Figi, F. A.: Personal communication.
10. Braasch, W. F.: Personal communication.
11. Crenshaw, J. L.: Personal communication.
12. Bumpus, H. C.: Personal communication.

large proportion of those of grade 2, unless the growth is too large, when they recommend diathermy or excision. All of the operable cases of grades 3 and 4 are treated by diathermy or excision. Epithelioma of the bladder of grade 4 with metastasis is as hopeless as the same grade of epithelioma of the lip, but fortunately does not, as a rule, seem to metastasize so rapidly. This may be due to the fact that in the bladder, as in the breast, stomach, testicle and cervix, there is a small proportion of locally highly malignant cancer that apparently metastasizes late or not at all. Hunt [13] believes that the most malignant primary cancers of the urinary bladder are usually situated at the base, and in these diathermy is the treatment of choice.

SUMMARY

The time is not far distant when not only physicians but also the patients and their relatives as well as life insurance companies will be interested in the grade of malignancy of cancer. If a surgeon knows the grade of malignancy of a cancer in addition to its size and situation, he is certainly in a better position to render more efficient treatment, and a more accurate prognosis than one without such knowledge. A patient with cancer of the lip or bladder of grade 1 type will most certainly be a better risk for life insurance than one with a cancer of grade 4 type, in either one of these situations.

DISCUSSION

DR. J. SHELTON HORSLEY, Richmond, Va.: Dr. Broders' classification is of value not only from a pathologic but from a clinical standpoint. It can be included in statistics of cures of cancer and make the statistics mean something. His grading of carcinoma explains why recurrence of some cancers is so much more frequent than the recurrence of others. Every few weeks I have occasion to avail myself of this classification of Dr. Broders. A striking instance that I can recall was the case of a man who came to me more than two years ago with an advanced cancer of the lower lip. He gave a history of having had it for several years. Frozen section showed squamous cell type of cancer of grade 1, according to the classification of Broders. The growth was so extensive that operation on this cancer, if it had been more malignant, would have been utterly unjustifiable. With this picture of low malignancy, and only a single metastasis in a lymph node in the neck, an operation was performed, and the patient has remained free from recurrence for more than two years.

DR. W. HUEPER, Chicago: I have worked out a method, based on the examination of 135 cases of carcinoma cervicis uteri, by which nine factors (special cell type of carcinoma, irregularities in size and shape of the cells, distinctness in outline of the cells, functional activity of cells, irregularities in size and shape of the nuclei, hyperchromatism, number of mitoses) covering the different signs of differentiation and anaplasia were evaluated in percentages which were expressed in numbers ranging from 1 to 4. The scheme was called "malig-

13. Hunt, V. C.: Personal communication.

nogram," and the sum of the numbers obtained, "malignancy index," being regarded as an index of the degree of histologic malignancy. The numbers of the index ranged from 10 to 40. Dr. Schmitz, the author of the clinical part of this work, compared the malignancy indexes with the clinical results and came to following conclusions: (1) The malignancy index shows no relation to the extension of the carcinoma. (2) All patients with a malignancy index above 30 died regardless of the degree of clinical extension and type of cells. (3) Cases with a malignancy index below 20 offer a good prognosis, if the disease is not yet generalized.

Laboratory and Clinical Notes

A MODIFICATION OF THE ZIEHL-NEELSEN STAINING METHOD FOR TUBERCLE BACILLI*

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One of the most valuable laboratory measures in the chain of diagnostic procedures in tuberculosis is the demonstration by staining methods of the acid-fast organisms in the sputum, urine, spinal fluid, etc.

Everyone familiar with this test is well aware of the fact that the number of positive results obtained is comparatively low. Frequently many specimens received for examination by the staining method may show negative results, but such specimens submitted to animal inoculation or cultivation may give positive findings. Furthermore, the tubercle bacillus, being pleomorphic, may be present in the smear in small or long rods, beaded forms, sometimes hair-like and non-acid-fast rods with a few acid-fast granules. Such a finding often considerably confuses the inexperienced worker.

During the course of a study on the acid-fast property of the tubercle bacillus, it was noticed that some electrolytes caused a marked precipitation of dye material from carbol-fuchsin during the process of staining. When such precipitation occurred, the bacilli were deeply stained and exhibited the well defined morphology of solid rods and a practical absence of beaded and hair-like forms. This was the point of departure from the original investigation which led to the development of the present staining method which embodies the major part of the Ziehl-Neelsen technic.

EXPERIMENTAL DATA

Ammonium chloride, ammonium sulphate, barium chloride, calcium chloride, magnesium chloride, ferric chloride, lead acetate, mercuric chloride, sodium chloride, sodium dichromate and secondary sodium phosphate all cause precipitation of the dye material from carbol-fuchsin when added in proper amounts. The precipitate comes down at room temperature, but dissolves when warmed to 28-30 C., and remains in solution if that temperature is maintained. Modified stains were prepared by adding these reagents until precipitation occurred and then dissolving the precipitate by gentle heating. These stains were then compared to the Ziehl-Neelsen stain and to each other by staining smears made from an old synthetic broth culture of human type H_{37} that contained mostly beaded and hairlike forms. Each of the modified stains caused an intensive staining, the bacilli standing out as thick, solid, dark red rods with practically a complete absence of beaded forms.

Since the precipitant used made no appreciable difference, sodium chloride was selected for the development of the modified stain. The amount necessary to give maximum staining was found to be 3 cc. of a 10 per cent solution per hundred cubic centimeters of carbol-fuchsin. Although this modified carbol-

* From the Research and Clinical Laboratory of The Edward L. Trudeau Foundation.

fuchsin precipitates at room temperature, it is stable if kept at incubator temperature, and keeps at least two months.

In this connection it may be recalled that the work of Koch,[1] Herman,[2] Andrejew,[3] Much,[4] Serkowski[5] and Gasis[6] shows their recognition of the importance of the mordanting action of electrolytes, although Andrejew, Much and Serkowski failed to incorporate them into their staining solutions.

STAINING TECHNIC

The technic for the modified stain, using the rapid method, is as follows: The slide is flooded with stain, steamed for four minutes and allowed to cool until the precipitate forms. This takes place in about two minutes, and may be hastened by gently blowing on the slide. The precipitate must be allowed to form, for on it depends the success of the method. It is then washed with tap water, decolorized for from one to ten minutes in acid alcohol (5 cc. of nitric acid, specific gravity 1.42, to 95 cc. of 95 per cent ethyl alcohol); washed with water, then two minutes in 95 per cent ethyl alcohol; washed again, counterstained with Loeffler's methylene-blue for one minute, washed, dried and examined.

In using the modified stain for the over night method, the staining is carried out in the incubator, and in the morning the jars containing stain and slides are allowed to stand at room temperature until precipitation takes place, or better still, in the icebox. The latter has the advantage of speed, as the precipitation is complete in half an hour. Good slides are obtained in from fourteen to twenty hours' staining. The decolorization and counterstaining are the same as for the rapid method.

The modified method described above was checked against the usual Ziehl-Neelsen technic on 200 specimens of sputum from unselected patients at Trudeau Sanatorium.

The following procedure was employed: The morning expectoration was collected in 2-ounce bottles, an equal volume of 4 per cent sodium hydroxide added, and the bottles well shaken and incubated at 38 C. for thirty minutes. The sediment was centrifuged out, the supernatant liquid discarded, from 2 to 4 cc. of approximately normal hydrochloric acid added to the residue in the centrifuge tube, shaken and again centrifuged. The supernatant liquid was discarded, the residue poured out on a slide and triturated between two slides by a gentle rotatory motion of the top one to insure a uniform mixture, and the slides then drawn apart. In this manner duplicate smears were obtained which gave an even distribution of material.

One set was stained by the Ziehl-Neelsen over night method for twenty hours and the other set by the modified stain for twenty hours in the incubator. Forty fields were examined on both slides, always starting with the mechanical stage at the same setting to insure examination of duplicate portions of the slides, and the number of bacilli and their morphology noted. When slides

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were found with eight or more bacilli to the field, only ten fields were examined. The results of the examination of 200 sets of duplicate slides follow:

Number of cases	200
Number of positives by the modified method	94
Number of positives by the Ziehl-Neelsen method	85
Total number of bacilli by the modified method	8,226
Total number of bacilli by the Ziehl-Neelsen method	4,722
Greater number of bacilli by the modified method	81
Greater number of bacilli by the Ziehl-Neelsen method	14

Of the eighty-five positives found by the Ziehl-Neelsen method, fifty showed beaded and hairlike forms, while with the modified method only two of the ninety-four positive cases exhibited these forms.

The finding of nine additional positive cases in 200, and one and seven-tenths times as many bacilli, together with the strikingly favorable change in morphology when using the same counterstain employed in the Ziehl-Neelsen method for control, establishes the superiority of the modified sodium chloride carbol-fuchsin.

At this point of the study it was suggested that the methylene-blue, being an intense stain, might mask a number of bacilli by super-imposition and also by rendering the heavier portions of the smear nontransparent.

Various counterstains were tried and brilliant green (1 per cent in 1:10,000 sodium hydroxide), selected since such a solution failed to stain tubercle bacilli in ten minutes, gave transparent smears and stained secondary organisms, pus and epithelial cells sufficiently to give nicely balanced fields in one to two minutes.

This counterstain is not to be confused with that of Andrejew[6] which was made up with potassium chloride and sulphuric acid, or with the malachite-green of Konrich.[7]

The completed modified method, employing the sodium chloride carbol-fuchsin and the brilliant green counterstain was now compared to the Ziehl-Neelson method on fifty-six unselected specimens, using the technic described above for collecting specimens and preparing and examining slides, with the following results:

Number of cases	56
Number of positives by the modified brilliant green method	21
Number of positives by the Ziehl-Neelson method	17
Total number bacilli by modified brilliant green method	1,918
Total number bacilli by Ziehl-Neelsen method	539
Greater number bacilli by modified brilliant green method	20
Greater number bacilli by Ziehl-Neelsen method	1

Of the seventeen positives found by the Ziehl-Neelsen method, thirteen showed beaded forms, while with the modified brilliant green method there were but two in the twenty-one positive cases.

CONCLUSION

A modified staining method is offered which without seriously complicating the Ziehl-Neelsen technic and still retaining its salient features has the following advantages:

1. Five per cent more positives than by the Ziehl-Neelsen method and many more times as many bacilli.

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7. Konrich, F.: Deutsche med. Wchnschr. **46**:741, 1920; **49**:852-854, 1923.

2. A much better defined morphology showing the bacilli as larger and deeper red solid rods with a practical absence of beaded and hairlike forms.

3. A counterstain which does not superimpose on tubercle bacilli in the time required for counterstaining, and, furthermore, gives slides of a sufficiently good transparency to make the acid-fast bacilli easily recognizable through the denser portions.

4. A more rapid method in that the time elapsing while awaiting the necessary precipitation to take place is more than made up in the amount saved due to the ease and sureness of examination.

General Review

THE NEUROTROPIC VIRUS

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The term neurotropic virus means all those invisible and filtrable viruses which show a special affinity to the central nervous system. Inoculated into the organism, they proceed along the nerves toward the central organ, where they find their strongest multiplication and produce the lesions deleterious to the whole organism. The tropism is, however, not limited to the nervous system in all cases, since some representatives of this group affect also the epithelial layers of the skin, the cornea and the mucous membranes. The affinity to the connective tissue and the parenchymatous organs is considerably lower. It would therefore be correct to replace the term neurotropic by the more general term ectodermotropic, since both the epithelial tissue and the nervous tissue are derived from the outer embryonic layer. Levaditi has consequently called the diseases produced by this group of viruses "neurotropic ectodermoses." To this group belong poliomyelitis, rabies, vaccinemia, herpes (which is considered by some authors to be the causative agent of epidemic encephalitis), finally herpes zoster (zona) and chickenpox. Those neurotropic viruses belonging exclusively to veterinary medicine, such as encephalitis enzootica, fowl plague and the like will be omitted in this review.

All these neurotropic viruses have the following characteristics in common: They are invisible, pass through filter candles, cannot be cultivated on artificial mediums and survive for a long time in glycerol as well as in the dry state. Furthermore, the anatomic lesions in the nervous system resemble each other very much, in spite of the clinical differences. Finally, the serum of the convalescent organism has the faculty to neutralize a moderate amount of the homologous virus, but it has no special prophylactic or curative value. These common characteristics justify the grouping of the viruses mentioned above, but there are, of course, many differences, which will be discussed. It must be emphasized that each of the viruses belonging to this group represents—in spite of all similarities—an absolutely specific antigen. Each virus can be recognized by the homologous immune serum, and there is no cross immunity to be observed in the animal experiment; in other words, the neurotropic viruses are related to each other systematically but not genetically.

THE HERPES VIRUS

Grüter has shown that the herpes of the human cornea can be inoculated into the rabbit's cornea and has in this way confirmed the opinion of some earlier clinicians that herpes is an infectious disease. Löwenstein, too, showed the etiologic identity of the corneal, cutaneous and progenital herpes and its immunizing qualities. Later Doerr and Voechting made the important observation that the herpes virus can proceed from the eye to the brain and produce a typical encephalitis. The same process, which is accompanied by an abundant multiplication and is as a rule fatal to the animal, can be produced by intracerebral inoculation.

The inoculation of the content of a fresh herpes vesicle from a human being into scarified rabbit's cornea is successful in the majority of cases. Failures occur occasionally owing to the low virulence of the material or to high individual resistance of the animal (Grüter). After an incubation time of from twenty-four to thirty-six hours, minute vesicles can be observed along the lines of scarification. They sometimes fuse and ulcerate later. The epithelial cells desquamate in large number, are edematous and show vacuolic degeneration of the plasma. In the nucleus, degeneration of the chromatin structure and formation of round or elliptical bodies are found, which can be seen in the unstained preparation and which have a special affinity for acid stains. These bodies multiply so much during the course of the disease that they enlarge the volume of the nucleus. Lipschütz described minute granules inside of these bodies, which he considers to be the specific agent of herpes. Goodpasture and Teague, who have found these bodies in all the lesions caused by this virus, assume that the inciting elements are enveloped by chromatin. Luger and Lauda, on the other hand, consider them to be only débris of the degenerated nucleus, but not the causative agent. These authors agree on the diagnostic value of the bodies, but further investigation in this line seems to be necessary.

The herpes bodies disappear from the epithelial cells of the cornea at about the same time as the virus does, that is, on about the seventh day after inoculation. The parenchyma of the cornea becomes turbid in the vicinity of the scarification, owing to infiltration by neutrophilic leukocytes which are replaced in the later phases of inflammation (about the second week) by lymphocytes, macrophages or plasma cells. The keratitis is as a rule accompanied by purulent desquamative conjunctivitis, frequently also by iritis.

If the virus proceeds to the brain, the encephalitis manifests itself by opisthotonic cramps of the muscles of the neck, manège-mouvements, trismus, pareses and salivation. The temperature of the animals becomes higher twenty-four hours before the symptoms appear and falls rapidly

just before death. The animals usually die after from two to four days of sickness. Recovery is rare. This is not always the typical course of the disease. There is another type in which pareses and paralysis predominate. The animals may even die without showing any special clinical symptoms after a marked multiplication of the virus in the brain (Doerr and Zdansky). Strains of low virulence sometimes produce chronic encephalitis following a previous keratitis; these animals die with cachexia after a lapse of from one to three months, with or without virus in the brain (Le Fèvre de Arric).

The anatomic lesions in the brain depend on the quantity of infectious material inoculated, the way of application, the virulence and some other factors which are not clear as yet. There are cases, reported especially by Lauda, which show minimal or no lesions in spite of the severest clinical symptoms of encephalitis. The anatomic lesions begin of course at the place of infection—after intracerebral inoculation in the cortex and in the meninges, after ocular infection in the mesencephalon, below the bottom of the fourth ventricle and in the medulla oblongata. The process of course does not remain limited to the place of infection, since the virus has the tendency to spread over the central nervous system. Cases of generalized encephalitis can be observed occasionally. In the ganglion cells there can be seen swelling of the nucleus and the protoplasm, sometimes formation of vacuoles and destruction of the cytoplasm. The changes inside the nucleus resemble closely the ones in the epithelial cells: the normal structure of the chromatin is loosened and in disorder and homogeneous oxychromatic masses are formed. Finally, the membrane of the nucleus is destroyed, and the débris is taken up by macrophages and glia cells(neuronophagia). Goodpasture and Teague consider the changes in the ganglions to be specific and of diagnostic value, a point in which they are not in accord with other authors (Cowdry and Nicholson). The changes in the brain start with hyperemia, edema and hemorrhages in the meninges and in the nervous substance. After that follows cellular infiltration, sometimes diffusely, sometimes in foci. The cellular elements are lymphocytes, leukocytes, plasma cells and macrophages, which contain cellular débris and erythrocytes. The infiltrates in the brain are mostly arranged in the form of cuffs around the blood vessels or of foci independent of the vessels. There can be seen also disseminated liquefied foci in acute cases. On the summit of the inflammation can be found an increased content of protein and an enlarged number of cells in the liquor, but no virus. In case the animals survive long enough, the cells of the exudate disappear—first, the polymorphonuclear leukocytes—and we find in their place a larger number of glia cells. Similar pictures were described also in human cases of encephalitis, a

fact which, however, does not justify the conclusion that the two diseases are identical.

The virus propagates from the eye to the brain along the nerves (Levaditi, Harvier and Nicolau, Goodpasture and Teague, Gaviati, Fontana, Friedenwald). Goodpasture and Teague in their excellent investigations have shown that the virus proceeds in the optic nerve when inoculated into the eyeball, but in the trigeminus when inoculated into the cornea. The virus proceeds—as the histologic findings show—in the axis cylinders, the passage through the perineural lymphatic vessels having probably minor, if any importance. Inoculated in any other place, the virus reaches the central nervous system in the same way, provided it has the necessary virulence. The initial clinical symptoms correspond to this part of the central nervous system, which is affected first by the virus (Marinesco and Draganesco, Goodpasture and Teague).

The effect of the intravenous infection is dubious, in most cases negative; some authors, however, have observed occasionally keratitis or encephalitis. Subdural or intracerebral inoculation produces encephalitis and meningitis with absolute regularity. Infections by contact sometimes occur when healthy animals are kept in contaminated stables (Grüter and Krumbach). The virus does not necessarily ascend toward the central nervous system; it can proceed also in the other direction. Blanc and Caminopetros have observed the occurrence of herpes keratitis in rabbits affected with encephalitis after scarification of the cornea. Szily, as well as Mariani, saw after infection of one eye metastases in the other eye. These metastases are probably due to the ascending of the virus in the optic nerve up to the chiasm and descending in the other optic nerve.

The many strains of herpes isolated from human cases show very different degrees of virulence for the rabbit; strains highly pathogenic for the rabbit have been found in mild human cases.

There is also no relation between the virulence for the cornea and the occurrence of encephalitis after corneal infection. The virulence of the virus can be increased to a certain degree by passages, but can by the same way, for unknown reasons, decrease or entirely disappear. Several authors report that the affinity to the brain can be raised by continuous passages from brain to brain, whereas the affinity for the cornea decreases or disappears. These experiments were, however, not confirmed by all observers, and should be continued. The virulence of the virus for human beings is apparently attenuated by frequent passages through the rabbit. This was proved by cutaneous (Teissier, Gastinel and Reilly) as well as by lumbar inoculation (Bastai and Busacca). A permanent attenuation of the virus by external

means as it is possible with the rabies virus has not been tried, as far as is to be seen from the literature.

The herpes virus can be found in man not only in the lesions, but sometimes also in the saliva of persons who are suffering from frequent attacks of herpes. In some persons the virus persists a long time after recovery. The strains isolated from such carriers have as a rule only a low virulence. The infectiousness of the blood during the disease has not been shown with absolute certainty. The respective findings of Bastai and Busacca are rather doubtful. The same authors are the only ones who have found the virus in the spinal fluid of a larger series of persons free from herpes. All other authors had negative results, with a few exceptions (Flexner and Amoss). It is worth while mentioning that in rabbits affected with encephalitis there is no virus in the spinal fluid. It is not known what causes recurrence in persons habitually suffering from herpes. The opinion that it is a latent infection, which assumes a chronic persistence of the virus in the blood and in the spinal fluid (Bastai and Busacca) has no experimental foundations. The same is true of the theory that it is an exogenic infection (Luger and Lauda) which assumes the ubiquitous presence of the virus.

The question of the etiologic identity of herpes and epidemic encephalitis is of the utmost interest. The hypothesis of Doerr and Schnabel has aroused an extensive discussion, which, however, has not brought a unanimous result. Doubtless the herpes virus in the rabbit can produce a disease which resembles human encephalitis (Le Fèvre de Arric). Of all infectious materials claimed to be the causative agent of encephalitis the ones of Doerr, Levaditi and their collaborators deserve special consideration. On the other hand, the herpes virus was found in persons suffering from encephalitis in a very small percentage as compared with the number of cases examined. This fact of course is not a very strong argument. But the herpes virus was also found in the spinal fluid of persons suffering from other diseases (Flexner and Amoss). Finally, there exists no relation between the incidence of corneal and cutaneous herpes and the encephalitis in man. It was never possible to produce encephalitis in man by cutaneous or lumbar injection of herpes virus. It seems that the hypothesis of Doerr and Schnabel has recently been supported by Perdrau's experiments. Perdrau stated that brain from human encephalitis, which—taken fresh—is free from virus, produces in the rabbit a typical encephalitis after being kept in glycerol for some weeks. These experiments certainly deserve to be repeated.

The herpes virus produces an immunity in the cornea of the rabbit which is fully developed after recovery and which as a rule lasts for

about six months (Doerr and Schnabel). Other authors, however, report successful reinoculation after a shorter time. These reinoculations ordinarily run a milder course and sometimes show allergic character. The height of the inflammation is reached after a few hours, and the cornea returns to normal after from four to five days (Fontana). It is still questionable whether there is a cross immunity between all the strains of herpes or whether the various strains can be brought into groups which represent antigenic unities. The immunity of the inoculated eye spreads over the whole organism in the course of one month; these animals cannot be infected either from the second eye or from the brain. It is, according to Doerr and Schnabel, far more difficult to obtain a general immunity by infection of the skin. It should be emphasized that immunity is accomplished only after a real infection, and it does not make any difference whether the symptoms were mild or severe. There is no possibility of getting any immunity by treatment with dead virus, as far as we know. The majority of authors were not able to find any germicidal substances in the serum of immune animals, but it seems likely that antibodies can be found with a certain regularity, provided the quantitative relations between serum and virus are taken into consideration (Flexner and Amoss). The serum has no therapeutic effect. Apparently there exist naturally resistant rabbits, according to the observation of Grüter.

HERPES ZOSTER (ZONA)

At the present time there cannot be any doubt that the herpes zoster is an etiologic entity to be separated from herpes simplex. Inoculation of the content of vesicles of zoster into the cornea or into the brain of rabbits has no effect. It was only Lipschütz who reported a positive result in a few cases in which he could observe a rapidly fading pustular eruption of the cornea, accompanied by conjunctivitis. He describes inclusion bodies inside of the nuclei of the epithelial cells (*Chlamydozoa*), which in his opinion are related to the virus. He finds the same bodies in material of human zoster cases. The presence of the bodies is, according to Lipschütz, more conclusive for a successful inoculation than the macroscopic symptoms. It seems to be by far easier to transplant the disease to human beings. Kundratitz inoculated zoster material into young children, and after an incubation time of from nine to fourteen days several vesicles developed at the site of inoculation resembling closely the vesicles of chickenpox. In some cases there was between the fifteenth and nineteenth day a generalization of the eruption which could not be distinguished from typical chickenpox. No relation between the eruptions and the innervation of the skin could be observed. Lipschütz was able to show in the cases

of Kundratitz the typical zoster bodies. These observations support Bokay's hypothesis of the etiologic identity of both diseases. In the serum of zoster and chickenpox have been found identical antibodies by complement fixation (Cornelia de Lange, Netter and Urbain). Furthermore, there has been described a cross immunity between both diseases in man. Tyzzer found the vesicles of chickenpox inclusion bodies which resemble the zona bodies of Lipschütz. It must be emphasized, on the other hand, that Gins with the content of chickenpox regularly obtained vesicles on the cornea of rabbits and inclusion bodies which were situated in the protoplasm of the epithelial cells and which could not be identified with the zoster bodies. Further examinations will be necessary before Bokay's hypothesis can be accepted entirely.

VACCINE VIRUS

The vaccine virus, like that of herpes, shows a special affinity for the skin, cornea and brain. But the affinity for the nervous system is considerably lower than that of the herpes virus. After an inoculation into the cornea, skin or testicle, a small quantity of the virus may enter the brain without producing encephalitis. The result of the experiment depends on the virulence and the quantity of the virus inoculated (Blanc and Caminopetros, Burnet and Conseil, Wassiljevski and Winkler). The resistance of the brain can be reduced so much by intracerebral injection of sterile salt solution or broth or by application of narcotics that encephalitis breaks out after cutaneous or corneal infection. The spreading from the periphery to the central nervous system takes place by way of the circulation, not inside the nerves. The vaccine virus intracerebrally inoculated into the rabbit produces a fatal meningoencephalitis with edema, hyperemia, cellular infiltrations and hemorrhages (Marie, Levaditi, Harvier and Nicolau). Condrea described inclusion bodies in the brain similar to the Guarneri bodies. Levaditi and his co-workers stated originally that the virus must pass several times through the testicle before it infects the brain. Recent investigations, however, have shown that many strains of vaccine virus produce a typical encephalitis after the first inoculation into the brain.

The classification in dermotropic and neurotropic strains seems to be without any importance in this case as in the case of the herpes virus. The virulence of the brain increases after continued passages up to a certain degree (virus fixe). This virus has the advantage of absolute sterility as it was first obtained by Noguchi's cultivation in the testicle, but the brain virus has not been found to be satisfactory in practice.

The infection produces immunity of the whole organism. The cornea has, according to recent investigations, no exceptional position, as it was assumed by von Prowazek. After inoculation into the skin,

immunity of the cornea develops from three to eight weeks later, apparently owing to the slow circulation in this tissue. The same is true for the skin when the virus is implanted into the cornea. The size of the infected area is of special importance for this effect (Grüter, Gins, Sato). Immunity of the cornea after cutaneous infection develops much quicker if the liquid of the anterior chamber is released several times (Nakagawa), or is replaced by immune serum (Camus), or if a solution of dionin, which increases circulation, is instilled into the eye (Winkler). Testicle and brain become immune after corneal or cutaneous infection. Immunity can be produced also by subcutaneous, intracutaneous or intrastomachal application and—in a low degree—also with virus killed by heat (Murata, Nakagawa). The prophylactic and therapeutic value of the immune serum is doubtful. Precipitating and complement-fixing antibodies can be found in vitro immediately after development of the immunity for a short time. Viricidal antibodies are present in the serum for about one year. After this time these antibodies return to the circulation after a second—even symptomless—infection. The duration of immunity is probably lengthened in this way. The immunity can be transferred from an immune animal to a normal one by transplantation of a patch of skin (Scarpellini).

POLIOMYELITIS

Neurotropic viruses in a stricter sense are the poliomyelitis and the rabies, in which the virus multiplies exclusively in the nervous system. The virus of poliomyelitis proceeds from the periphery toward the central nervous system along the nerves, probably in the nervous substance as well as in the perineural lymphatic vessels. Flexner and Amoss, Leiner and Wiesner found the virus also in the lymphatic glands near the site of inoculation. It is, however, not certain whether the virus is able to multiply in this tissue. Monkeys can be infected from the subcutis or from the mucous membranes—provided the virulence is high enough—but this way of infection is not as reliable as the intracerebral one. According to Flexner and Amoss, the virus after peripheral insertion is more likely to reach the central nervous system when a lumbar injection of normal horse serum or Ringer's solution is given. In contrast to all other neurotropic viruses, no infection takes place after corneal inoculation of poliomyelitis virus.

The greatest multiplication of the virus takes place in the gray substance of the spinal cord, where well marked histologic lesions can be found in the greatest number. As in encephalitis, these lesions consist in edema, hemorrhages and cellular infiltrations, partly arranged around the vessels, partly in independent foci. The anatomic changes in poliomyelitis ordinarily begin in the lumbar part of the spinal

cord and sometimes extend as far as to the cortex. The infiltrations consist in the acute stage of polymorphonuclear leukocytes. Later mononuclear cells and fixed tissue cells predominate. The phenomenon of neuronophagia can be especially well observed in poliomyelitis.

Under the influence of the virus, the ganglions show swelling, formation of vacuoles and fading of the Nissl bodies. Leukocytes and macrophages gather around the degenerated cell and invade it, liquefying the plasma and destroying the nucleus. As to the remaining débris, phagocytosis by macrophages occurs. In case of recovery the focal infiltrations and necroses are replaced by scar tissue. The spinal fluid during the disease has an increased pressure and is slightly turbid because of the larger number of cells. Changes in organs other than nervous are not very distinct. Flexner, Peabody, Draper and Dochez described hyperplastic changes in the lymphatic apparatus and necrotic foci in the liver followed by cellular infiltration and regeneration.

According to Flexner and Noguchi, the virus can be cultivated under anaerobic conditions (in the medium suggested by Noguchi) in the form of very small corpuscles (globoid bodies).

No virus can be found in the blood, spinal fluid and parenchymatous organs. Of the utmost importance is the observation of Flexner and Lewis that the mucous membranes of the nose and throat and the saliva sometimes contain the virus after intracerebral inoculation. According to Osgood and Lucas, the virus survives for six months on the mucous membrane of the nose. It is generally acknowledged that for the propagation of the virus healthy carriers and mild chronic cases are of the greatest importance. Other ways of dissemination (dust, milk, insects) play a minor rôle, if any. The virulence of certain strains of poliomyelitis is varying widely (Flexner and Amoss) without any traceable reason.

The immunity after the disease seems to be of limited duration, since reinfections in man have been observed several times. It is, however, hard to say whether these cases were relapses due to the virus persisting in the organs or whether they were exogenic reinfections. It is likely that both may occur occasionally. Levaditi and Stanescu described cases in monkeys which must be interpreted as true relapses. The serum of the convalescent man or monkey neutralizes the virus in vitro (Landsteiner and Levaditi, Netter and Levaditi). It is a question whether the serum kills the virus in vitro or whether the virus is sensitized by the serum and phagocytosed rapidly inside the body. These antibodies are, according to Flexner and Clark, transitory also in the spinal fluid. They can be found in a smaller quantity in mild, clinically doubtful cases, and can be used for diagnostic purposes.

For active immunization, all the procedures which proved useful in rabies have been tried. The injection of dried virus (Landsteiner and Levaditi), of virus carefully heated to 50 degrees (Roemer, Joseph), of diluted virus (Flexner and Lewis), of sensitized virus (Landsteiner and Levaditi) have been tried. Successful immunization of monkeys has been obtained by every one of these procedures, but there were so many failures, and the danger of infection is so great that there is no hope for the time being to use these methods for the immunization of man. Furthermore, the time necessary for the treatment is much longer than the incubation time of the disease. Dead virus has no immunizing qualities. Flexner and Amoss have isolated a strain of poliomyelitis from a fatal human case, which immunized monkeys after a very mild course of the disease. The immune serum has, according to the experiments of Flexner and Lewis, marked preventive qualities if administered early enough into the spinal canal. Some French authors also report favorable therapeutic results in man with this serum.

RABIES

The characteristics of the rabies virus and its manner of propagation resemble so much the conditions of poliomyelitis that only a few words need to be said. The investigations of the last years have not brought forth much essentially new in this field.

It is possible to infect not only intracerebrally but also subcutaneously, intracutaneously and corneally without any noticeable symptoms on the site of infection. The effect of the intravenous infection is doubtful, whereas the intraperitoneal inoculation produces immunity in most cases without any previous clinical symptoms. Even the contamination of the intact skin occasionally may lead to the typical disease. This virus also reaches the central nervous system by way of the nerves. It has seldom been found in the blood. Once in the central nervous system, the virus multiplies and produces the typical anatomic lesions which are responsible for the clinical symptoms. There are, however, cases in which the virus remains latent in the brain without producing any symptoms. But the disease may break out later, following nonspecific influences such as trauma, cold and the like. The saliva of infected dogs contains the virus several days before the onset of the disease, and in case of recovery several days after the disappearance of the symptoms. It is not yet established whether the virus reaches the salivary glands by way of the nerves or by the lymphatic vessels.

It seems superfluous to speak extensively about the generally known facts of active immunization in rabies, especially as relatively little progress has been made in this field since Pasteur's investigations. The serum of immunized organisms in rabies as in poliomyelitis contains

viricidal antibodies which neutralize the virus in vitro. The serum administered to the organism has neither prophylactic nor curative qualities. But the method of immunization with sensitized virus—it is with virus loaded with antibodies—suggested by Marie has proved to be useful. It is still questionable whether the attenuation of the virus by drying, carbolizing, etc., is brought about by rarefication or by a qualitative modification of the germs. The majority of authors are inclined to believe the first hypothesis. In the same way it is impossible to say anything definite about the relation between the virus of the street to the virus fixe. It is likely that a process of mutation plays a rôle.

Levaditi, Nicolau and Schoen are of the opinion that the elementary corpuscles situated inside the Negri bodies can be interpreted as spores of *Microsporidium.* Manouelian and Viola called this hypothetic *Microsporidium, "Encephalitozoon rabiei."* Whether these corpuscles can be identified with the organisms cultivated by Noguchi remains to be settled by further investigation.

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Notes and News

Promotions and Appointments.—Dr. Max Pinner, serologist, Chicago Municipal Tuberculosis Sanitarium, has accepted the directorship of the laboratory of the Municipal Tuberculosis Sanatorium of Detroit at Northville, Mich.

Professor Leonor Michaelis, of the University of Berlin and visiting professor of biochemistry in the Aichi University of Nagoya, Japan, has been appointed resident lecturer in research medicine in the Johns Hopkins University for a period of three years. Dr. Michaelis has recently arrived from Japan and has begun his research work in biophysics at the Johns Hopkins Hospital.

George H. Smith, of the department of bacteriology in Yale University, has been promoted to full professorship.

Dr. I. J. Kligler, formerly of the Rockefeller Institute, and for the last three years director of the malaria research unit attached to the Department of Health of the Palestine government, has been appointed head of the new department of hygiene established at the Hebrew University in Jerusalem.

Arthur L. Bloomfield, associate professor of medicine, Johns Hopkins University Medical School, has been appointed professor of medicine at Stanford University Medical School, San Francisco, beginning with the year 1926-1927. Dr. Bloomfield graduated from the medical department of Johns Hopkins in 1911.

The Andrew Todd McClintock Foundation.—This foundation comprises a bequest of $500,000 by the widow of Dr. Andrew Todd McClintock for the study of alimentary disease. Eventually the principal will go to Cornell University. In the meantime, the activities of the foundation will be directed by Dr. John William Draper of New York. Dr. McClintock (1885-1923) was a physician of unusual powers and achievements who practiced in Wilkes-Barre, Pa., where he was born. He was interested especially in bacteriology and left the manuscript of a book on "Pleomorphism in Bacterial Protoplasm, a Study in Psittacosis," which has been published as the first volume of the *Archives of The McClintock Foundation.*

Death of Julius Bartel.—Dr. J. Bartel, associate professor of pathology in the University of Vienna, has died, aged 52. His early work dealt with the genesis and immunity of tuberculosis. His best known work is that on status thymicolymphaticus (Paltauf) and status hypoplasticus (Bartel's disease), whereby he stimulated the study of the constitution in relation to disease. One of his last articles dealt with the problems of the constitution (*Ztschr. f. Konstitutionslehre* **11**:127, 1925).

Award for Work on Erysipelas.—The Women's Educational and Industrial Union of Rochester, N. Y., has awarded $500 to Dr. Konrad M. Birkhaug in recognition of his work on the immunology and specific treatment of erysipelas. Dr. Birkhaug is associate in bacteriology in the school of medicine and dentistry of the University of Rochester and resident bacteriologist in Strong Memorial Hospital.

The Tunis Pasteur Institute.—*Archives de l'Institut Pasteur de Tunis* for April, 1926 (vol. 15, no. 1) gives a good description of the Tunis Institute, and summarizes interestingly the important work there accomplished or under way on typhus fever, recurrent fever, measles, undulant fever, kala azar trachoma and other diseases of particular interest to students of tropical medicine.

Mills to Mayo Clinic.—Dr. Ralph G. Mills has resigned as professor of pathology in the University of Colorado and has accepted a position on the pathology staff of the Mayo Clinic and a professorship in pathology in the University of Minnesota.

Klotz to Study Yellow Fever.—Dr. Oskar Klotz, professor of pathology and bacteriology of the University of Toronto is in Lagos, West Africa, where he will investigate yellow fever for six months on behalf of the Rockefeller Foundation.

Study of Tropical Diseases.—Richard P. Strong, professor of tropical medicine, Harvard University Medical School, is leader of an expedition to Liberia for the purpose of studying tropical diseases and the effects of certain remedies on them.

Abstracts from Current Literature

Pathologic Physiology

THE RESPIRATORY METABOLISM IN INFANCY AND IN CHILDREN. III. GLYCOGEN STORAGE IN CHILDREN. S. Z. LEVINE, J. R. WILSON and H. RIVKIN, Am. J. Dis. Child. **31**:496, 1926.

The total carbohydrate oxidized during short periods of fasting preceded by diets with sufficient carbohydrate to ensure glycogen storage varied little in two normal children, one obese child and one with cyclic vomiting. In a child with diabetes mellitus, however, the utilization of carbohydrate per square meter of body surface was decidedly lower, probably on account of a defective mechanism for glycogen storage. There was no evidence in these results that a diminished capacity for glycogen formation might be a factor in the susceptibility to ketosis associated with cyclic vomiting.

E. B. PERRY.

A COMPARISON OF THE PIGEON AND THE RAT AS TEST SUBJECTS FOR VITAMIN B. C. N. LAIRD, Am. J. Hyg. **6**:201, 1926.

The recorded data bear on the question whether the pigeon and the rat test procedures for detecting vitamin B give the same information.

Extracts have been prepared by the application of several solvents to wheat germ. These have been administered, singly and in combinations, to pigeons and rats brought into the conditions usually demanded for testing for the antineuritic substance, vitamin B. The data show how these two test subjects respond to these preparations.

The results clearly show that some preparations give positive results with one species and negative ones with the other, and vice versa.

A consideration of the data recorded does not permit of definite conclusions as to whether the vitamin B requirements of the bird are simpler than are those of the rat.

It is impossible to decide, on the basis of existing data, as to whether or not what is now known as vitamin B is a single substance or is of multiple nature.

AUTHOR'S SUMMARY.

THE NUTRITIONAL REQUIREMENTS OF NURSING MOTHERS. THE EFFECT OF A DEFICIENCY OF THE ANTIRACHITIC VITAMIN ONLY IN THE DIET OF THE MOTHERS UPON THE DEVELOPMENT OF RICKETS IN THE YOUNG. AGNES H. GRANT and MARIANNE GOETTSCH, Am. J. Hyg. **6**:211, 1926.

Rickets is primarily due to a lack of the antirachitic vitamin, and will develop when a lack of the vitamin is the only deficiency in an otherwise adequate diet.

The diet of the mother is an important factor in increasing or decreasing the resistance of the young to the effects of diets which are deficient in the antirachitic vitamin.

Under ordinary circumstances rickets does not develop in the young of well nourished mothers when a lack of the antirachitic vitamin is the only deficiency in their diet.

The rapidity with which the disease develops and the severity of the lesions depends on the degree to which the mother's reserve of the antirachitic vitamin has been depleted.

After the mother's vitamin reserve has been depleted until the young are made very susceptible to rickets, she can be brought back to normal by increasing the vitamin content of her diet.

The diet of the mother can be made to furnish enough vitamin to prevent the depletion of her reserve of this factor, and allow her to raise fourth litters that are normal in resistance.

AUTHORS' SUMMARY.

THE NUTRITIONAL REQUIREMENTS OF NURSING MOTHERS. THE EFFECT OF LOWERING BOTH THE ANTIRACHITIC VITAMIN AND CALCIUM IN THE DIET OF THE MOTHER UPON THE DEVELOPMENT OF RICKETS IN THE YOUNG. AGNES H. GRANT, Am. J. Hyg. **6**:228, 1926.

The effects of lowering both the antirachitic vitamin and calcium of the mother's diet are seen in the retarded growth of the young when they are kept on a uniform low calcium, low vitamin diet, as well as in the change in the type of rickets which develops on this diet, and in the increasing readiness with which the disease attacks the spine.

The rate of growth of the young after weaning is correlated with their weight when they are weaned, and on the length of the interval before they begin to develop signs of rickets. The weight curves flatten as the disease develops, until finally all growth ceases, and the weight curves become straight lines.

The age at which the young begin to develop signs of rickets, the rapidity with which the disease develops, and the severity of the final lesions depend more on the diet of the mothers than on the weight of the young when they are weaned; the largest and most resistant of the young from mothers on rachitic diets develop rickets at an earlier age, and in a more severe form, than the lightest weight young from mothers on a complete diet.

The type of rickets which develops in young that are kept on a uniform low calcium, low vitamin diet changes from the slow progress of the chronic type of this disease to the rapid development of the acute types, as the vitamin and calcium content of the mothers' diets are progressively altered from the diets which are rich in both calcium and vitamin to those which are deficient in both of these factors.

The increasing readiness with which rickets attacks the spine in the young that are kept on the uniform rickets producing diet is a fairly accurate index of the kind and amount of the calcium and vitamin deficiency in the mother's diet.

AUTHOR'S SUMMARY.

VARIATIONS IN THE FAT-SOLUBLE VITAMIN CONTENTS OF EGGS RESULTING FROM DIFFERENT METHODS OF PRESERVATION. IRA A. MANVILLE, Am. J. Hyg. **6**: 238, 1926.

Three lots of fresh eggs were gathered from the same source at the same time of the year. One lot was placed in cold storage for one year; another was placed in water glass for eighteen months, and the third lot was used to establish standards by which the first two could be compared. The ether extract of the yolks was fed in amounts ranging from 0.25 per cent to 5 per cent.

By comparison of the resulting data it was determined that cold storage eggs lose not less than 75 per cent of their vitamin value; water glass eggs

50 per cent and frozen eggs something less than 50 per cent. It was found possible to maintain rats in a fairly normal condition by as low an amount of egg oil as 18 mg. a day. It is probable that this can be reduced still further.

By feeding graduated amounts of egg oil (fat-soluble vitamin), it was found that there is an optimal level at which this vitamin can be fed, and that apparently as much harm results from an excess as from a partial or complete lack of this principle. Spring eggs contain more vitamin than winter eggs, and it appears that hot-house vegetables (lettuce) have less value than vegetables which have been grown in the field.

AUTHOR'S SUMMARY.

THE METABOLISM OF OBESITY. IV. THE DISTRIBUTION OF ENERGY PRODUCTION AFTER FOOD. C. C. WANG and S. STROUSE, Arch. Int. Med. **36**:397, 1925.

The work of Wang and Strouse is concerned with the energy derived from the various nutrients of obese, normal and thin people after the ingestion of meals high in protein, carbohydrate and fat, respectively. After ingestion of protein, obese people have a tendency to derive their energy from carbohydrate, whereas thin and normal people use less carbohydrate than during starvation. Calories derived from fat decrease in the obese after the meal, but show little change in thin and normal persons. The latter groups show a decided rise in calories derived from protein after the meal, but protein consumption is little affected in the obese. The authors believe that there is little specific dynamic action of protein in obese people. All subjects derive more energy from carbohydrate after the ingestion of a high carbohydrate meal, and less from fat. There is no relation between pulse rate and energy production computed on the basis of heat produced per square meter of body surface.

S. A. LEVINSON.

THE EFFECT OF LIVER DAMAGE ON CHOLECYSTOGRAPHY IN DOGS BY THE USE OF SODIUM TETRA-IODOPHENOL-PHTHALEIN. B. M. FRIED and L. R. WHITAKER, Arch. Int. Med. **37**:388, 1926.

The purpose of this study has been to determine the toxicity of sodium tetra-iodophenolphthalein in dogs in which the liver was damaged by the use of chloroform as an anesthetic, and the degree of excretion of the drug by a liver thus damaged as determined by cholecystography. The results have shown that a moderately damaged liver does not interdict the use of sodium tetra-iodophenolphthalein, for the animals with a liver so damaged tolerate the drug apparently as well as normal animals. Because of the much smaller amount of sodium tetra-iodophenolphthalein used as a routine in patients (one-fourth) than used with safety on dogs known to have more or less extensive hepatic damage, the existence of presumed or obvious hepatic disease in human beings should not necessarily preclude the employment of the drug for purposes of cholecystography in the clinic.

S. A. LEVINSON.

NOTES ON THE CHEMISTRY AND PHYSIOLOGY OF THE ANTI-PRESSOR FRACTION FROM HEPATIC TISSUE. A. A. JAMES, N. B. LAUGHTON and A. B. MACALLUM, Proc. Am. Soc. Biol. Chem., J. Biol. Chem. **67**:6, 1926.

A water-soluble substance may be extracted from liver tissue which causes a sustained fall in blood pressure, especially in clinical hypertension. The substance is ether-soluble and acetone-insoluble, gives no biuret reaction, no

test for histamine, and no crystals of choline with iodine. The site of action is not on the capillaries as with histamine. There is no peripheral nor capillary dilatation. There is a venous engorgement, together with a slowing of the blood stream, in the veins and arterioles of the mesentery.

ARTHUR LOCKE.

CLINICAL CALORIMETRY. XL. THE EFFECT OF THE ABSENCE OF SWEAT GLANDS ON THE ELIMINATION OF WATER FROM THE SKIN AND LUNGS. H. B. RICHARDSON, J. Biol. Chem. **67**:397, 1926.

The sweat glands constitute an emergency apparatus which is called on only under exceptional conditions. A person possessing no sweat glands may eliminate a normal amount of water vapor when in a resting condition, but the amount is not increased during exercise or exposure to heat as it is in normal persons, and the body temperature may consequently rise under the latter conditions. Less than 30 per cent of the water vapor eliminated from a person lacking sweat glands comes from the lungs. The remainder comes from the skin independently of sweat glands.

ARTHUR LOCKE.

THE BASAL METABOLISM OF GIRLS. K. BLUNT, J. TILT, L. MCLAUGHLIN and K. B. GUNN, J. Biol. Chem. **67**:491, 1926.

Comparisons of basal metabolism on the basis of calories per square meter show less variation from the average, among children of different builds, than do comparisons on the basis of calories per kilogram.

THE EFFECT OF SLEEP ON URINARY CHLORIDES AND p_H. G. E. SIMPSON, J. Biol. Chem. **67**:505, 1926.

The urinary p_H and the amount of chloride excreted per hour are markedly increased on waking from the night's sleep. The increases are not the result of changes in urine volume.

ARTHUR LOCKE.

EFFECTS OF SUBTOTAL GASTRECTOMY ON GASTRIC SECRETION. EXPERIMENTAL STUDIES BY AID OF A PAWLOW POUCH IN DOGS. SIDNEY A. PORTIS and BERNARD PORTIS, J. A. M. A. **86**:836, 1926.

The gastric secretion in dogs after a subtotal gastrectomy shows an absence of free acid but a high combined acidity, whereas the secretion from a Pawlow pouch, representing a similar part of the stomach, continues to secrete free acid after resection.

The results indicate that the factor of neutralization plays the most important rôle in explaining the absence of free acid observed experimentally and clinically in the gastric secretion after subtotal gastrectomy.

The artificial achylia produced may establish an entirely new and possibly harmful bacterial flora of the gastro-intestinal tract, with consequent gastro-intestinal abnormality.

AUTHORS' SUMMARY.

THE PATHOLOGIC PHYSIOLOGY OF EXPERIMENTAL GANGRENOUS PANCREATITIS. LUCIA E. TOWER, J. A. M. A. **86**:1112 (April 10) 1926.

In an experimental investigation of acute gangrenous pancreatitis brought about in dogs by ligation of the pancreatic vessels, Tower found that the destruction of the pancreatic tissue in situ was associated with marked toxemia and with the death of the animals in from 36 to 100 per cent in the different

series of experiments, depending on the amount of tissue destroyed. In animals in which equal amounts of pancreatic tissue, wrapped in omentum and placed in the peritoneal cavity, were allowed to undergo necrosis and autolysis, no deaths occurred. Bacteria, probably derived from the upper intestinal tract, were found to be present uniformly in freshly removed normal pancreas and in pancreatic tissue which was allowed to undergo necrosis in situ or in the peritoneal cavity. Since the elements of bacterial activity and of pancreatic autolysis and necrosis were common factors in all the series of animals, those which recovered as well as those which died, the inference is drawn that these factors are not the essential ones in the toxemia of acute gangrenous pancreatitis. In the animals that died the upper gastro-intestinal tract was dilated, the appearance being that of paralytic ileus. Tower concludes that the toxemia and death in acute gangrenous pancreatitis are not due directly to toxins of bacterial or pancreatitic origin, but to toxemia of gastro-intestinal origin brought about probably by the local action on the upper intestinal tract of substances derived from the gangrenous pancreatic tissue. Treatment of acute pancreatitis by those methods which have been found useful in high intestinal obstruction, rather than by drainage of the pancreas, is suggested.

O. T. Schultz.

Experimental Bone Marrow Reactions. I. Anemia Produced by Collargol. Gulli Lindh Muller, J. Exper. Med. **43**:533, 1926.

The effect produced by the intravenous administration of collargol on the bone marrow of rabbits varies directly with the amount of collargol injected, and three fairly well defined stages could be recognized: an initial stage after comparatively few and small doses, with erythrocytic and endothelial hyperplasia in the bone marrow and with evidences of this stimulation in the peripheral blood in the form of young erythrocytes and normoblasts; an intermediary stage which followed the injection of larger amounts of collargol, and which was characterized by a predominant myeloid hyperplasia; a final stage with marked bone marrow aplasia and with colloidal silver deposited in endothelial cells, as well as in clasmatocytes. This was associated with a high grade anemia with low color index, resembling aplastic anemia in its main features. This stage terminated fatally.

There was no evidence of injury to blood cells in the peripheral circulation. The erythrocytic bone marrow aplasia was present before any appreciable decrease of red blood cells was found in the peripheral blood.

The results were less clear-cut in a series of rats, but anemia of a similar type was produced in all animals when sufficiently large doses were injected. Splenectomy did not alter the course in rats materially.

It is fair to conclude that the cause of the anemia produced may be sought in the deviation of the parental endothelial cell toward clasmatocyte formation at the expense of the development of erythrocytes.

It is suggested that the results may be offered in support of the theory of the endothelial origin of both clasmatocytes and red blood cells.

Author's Summary.

The Mortality in Important Surgical Diseases, Especially Appendicitis. A. Murat Willis, Surg., Gynec. & Obst. **42**:318 (March) 1926.

The records of the Bureau of Vital Statistics show that while there has been a decrease in mortality rate of such conditions as hernia, intestinal obstruction, surgical diseases of the kidney and pelvic inflammation, there has

been a steadily mounting death rate in others. Thus, in the five year period, 1901 to 1905, the number of deaths per hundred thousand from gallstones was 2.2 per cent; in the succeeding years it rose steadily, until in 1922 it showed an increase of 77 per cent. In the same period of time, the mortality rate from gastro-intestinal diseases increased 72 per cent; that from appendicitis almost 31 per cent; while the mortality rate from thyroid disease showed the stupendous increase of over 250 per cent. The reasons for this condition are chiefly: first, the presence of a constantly increasing number of surgeons with little experience in important surgical procedures who are resorting to operative therapy; second, lack of uniformity in teaching as regards appropriate treatment in such conditions as appendicitis and especially gastroduodenal ulcer.

M. L. PARKER.

CHONDRODYSPLASIA. WALLACE H. COLE, Surg., Gynec. & Obst. **42**:359 (March) 1926.

The author reports a case of chondrodysplasia in a girl, aged 11 years, and reviews the literature on the subject. He finds several types of cases in the group of chondrodysplasias. One of these is "Ollier's disease," used to designate those cases of cartilaginous dystrophy with or without cartilaginous tumor or exostosis formation which show an asymmetrical involvement of the body as the outstanding clinical feature. Several cases of symmetrical involvement are on record, and the broader term, chondrodysplasia, should be applied to these. The gradation of reported cases between those of frank multiple cartilaginous exostoses on the one hand, and those with no change in anything except the internal architecture of the bones, is so varied and irregular, that a definite classification of chondrodysplasias is still impossible. The possibility that the widely different findings in some of the cases are only manifestations of different stages of the same condition must be considered.

M. L. PARKER.

BENZINE POISONING. N. SCHUSTROW and E. SALTIS-IOWSKAJA, Deutsches Arch. f. klin. Med. **150**:271, 1926.

HABITUATION TO BENZINE. Ibid., p. 277.

On inhalation of petroleum ether, rabbits and guinea-pigs develop emaciation, aplastic hemolytic anemia, increased fragility of red corpuscles and leukopenia. The serum in such animals contains less cholesterol than normally. It is assumed that benzine acts on the lipoids. Animals acquire increased resistance to benzine, but this resistance disappears after injecting 0.1-0.2 Gm. of lecithin in olive oil, and it seems fair to infer that resistance is due to loss of fat and consequent diminished absorption by the blood.

INVESTIGATIONS INTO THE VALUE OF THE PHENOLSULPHONPHTHALEIN TEST IN RENAL AND CIRCULATORY DISEASES. C. LUNDSGAARD and EGGERT MÖLLER, Acta med. Scandinav. **63**:242, 1926.

CONTINUED INVESTIGATIONS INTO THE EXCRETION OF PHENOLSULPHONPHTHALEIN BY THE KIDNEYS: THE COURSE OF THE EXCRETION CURVE AND THE TOTAL EXCRETION IN CIRCULATORY AND LIVER DISEASES. Ibid., p. 268.

AN INVESTIGATION INTO THE FATE OF PHENOLSULPHONPHTHALEIN IN THE ORGANISM. Ibid., p. 277.

The authors carried out phenolsulphonphthalein tests on persons with circulatory, renal, and liver diseases, using intravenous injection of 6 mg. accompanied by 1 liter of water by mouth, and measuring the dye and water excretion for ten hours afterward. They found decreased dye excretion in hypertension without renal lesions, in heart disease with and without decompensation, and in renal disease, except nephrosis. Diminished water excretion seemed to account for low output of dye in some cases. They conclude, therefore, that the phenolphthalein test can be used as a criterion of renal disease only if the other conditions can be excluded, and that it is an early and valuable sign of circulatory failure. Following the dye excretion, for ten hours they found a delayed and diminished excretion in circulatory disease, and especially in liver stasis and diseases of the liver, indicating that this organ has something to do with the fate of the dye. Normally from 68 to 94 per cent was excreted in the urine. Of the remainder, part was recovered from the feces in one third of the patients, some appeared to be absorbed from the intestine, and some was altered there to colorless compounds. In normal persons, dye was found in the bile; in persons with liver disease, none could be detected there.

B. R. LOVETT.

INFLUENCE OF INSULIN ON THE GLYCOGENIC FUNCTION OF THE LIVER. PAUL SCHNEIDER, Ann. d'anat. path. méd. chirurg. **2**:513, 1925.

In the mouse insulin did lead to increase of glycogen in the liver. Rabbits showed a gradual increase of glycogen in the liver up to the fifth hour after injection. In dogs with pancreatic diabetes the liver had no glycogen, but when insulin was given glycogen appeared in the liver; in the normal dog the amount of glycogen in the liver increased after injections of insulin.

Pathologic Anatomy

BILIARY CIRRHOSIS: REPORT OF A CASE WITH ATRESIA OF THE INTRAHEPATIC BUT WITHOUT ATRESIA OF THE EXTRAHEPATIC BILE DUCTS, AND WITH A STUDY OF ITS METABOLISM. LEONARD G. PARSONS and EVELYN M. HICKMANS, Am. J. Dis. Child. **31**:459, 1926.

A case of biliary cirrhosis is described in which there is evidence of obstruction of the bile ducts but not in their extrahepatic course.

The argument is brought forward that this case supports the view that the hepatic cirrhosis occurs in at least as early a stage of the disease as the changes in the bile ducts.

Metabolism balance experiments show that fat is well split; there is an increased formation of fatty acid, and fat absorption is poor; nitrogenous absorption is good; there is a negative balance for calcium; phosphorus absorption is good; a great proportion of the excretions of phosphorus is via the urine.

The presence of large quantities of unabsorbed fat in the intestine—owing to the exclusion of bile—resulted in a negative calcium balance and a deviation of phosphorus to the urine, but had no effect on the absorption of nitrogen.

AUTHORS' SUMMARY.

CHRONIC INTERSTITIAL HEPATITIS. GEORGE F. MUNNS, Am. J. Dis. Child. **31**: 469, 1926.

A case is described in an infant in whom the first sign of the disease appeared on the eighteenth day of life. The cirrhosis in this case was not due to congenital syphilis or atresia of the bile ducts. The author was able to find only two similar cases outside of cases reported from India.

THE MODE OF DEATH IN VARIOUS TYPES OF HEART DISEASE. FREDERICK A. WILLIUS, Am. J. M. Sc. **171**:480, 1926.

In a review of 330 cases in which death occurred as the direct result of cardiac disease, clinically or pathologically determined, the types were as follows: (1) arteriosclerotic cardiac disease, 25 per cent; (2) myocardial infarction, 11 per cent; (3) hypertensive cardiac disease, 12 per cent; (4) cardiac hypertrophy associated with obesity, 0.6 per cent; (5) acute myocarditis, 0.3 per cent; (6) cardiac failure from mechanical causes, 0.6 per cent; (7) chronic endocardial valvular disease, 28 per cent; (8) bacterial endocarditis, 9 per cent; (9) pericardial disease, 5 per cent; (10) cardiovascular syphilis, 8 per cent; (11) congenital cardiac disease, 1 per cent. Sudden death occurred in 125 cases (38 per cent), while death from gradual cardiac failure occurred in 205 cases (62 per cent). Embolic phenomena occurred in fifty-eight cases. Necropsy was performed in 85 per cent of the cases reported.

AUTHOR'S SUMMARY.

INTERSTITIAL GLAND CELLS IN THE HUMAN OVARY. BERTRAM D. LEWIN, Am. J. M. Sc. **171**:518, 1926.

Among forty-three pairs of ovaries from psychotic cases, two ovaries, each from a different case, showed in the hilum a small island of cells identical in appearance with the interstitial gland cells of the testis. The clinical diagnosis in both cases was "senile psychosis." No functional features were to be correlated with this finding. If the cells exerted a "male" influence, the fewness of their number, or the presence of general senility, prevented this influence from manifesting itself. The possibility of overlooking the presence of such an island when the ovary is removed in the usual routine manner at necropsy, is pointed out.

AUTHOR'S SUMMARY.

HYPERTROPHY, CONGENITAL, OF THE LEFT SHOULDER GIRDLE, ARM AND HAND, WITH NAEVUS AND VARICOSE VEINS. G. G. WAKEFIELD, Am. J. M. Sc. **171**: 569, 1926.

A case of the condition is described, with a review of the literature.

REPORT OF A CASE OF ECTOPIA VISCERUM, RACHISCHISIS, MALFORMATION OF THE SACRUM, PELVIS INVERSA, HYPOPLASIA OF THE THORACIC DUCT, AGENESIS OR HYPOPLASIA OF VARIOUS ABDOMINAL VISCERA AND PLACENTA PREVIA. R. MILLS and B. WALPERT, Am. J. Obst. & Gynec. **11**:10 (Jan.) 1926.

Mills and Walpert report a combination of abnormalities occurring in the seven months' fetus of a multipara having a central placenta previa. The upper half of the body was normally developed. The anterior abdominal wall was absent, being replaced by a membrana reuniens; there was complete herniation of all the abdominal contents. The spinal column terminated abruptly at the lumbosacral junction with acute angulation and lateral displacement of a

deformed sacrum and a backward displacement and deformity of the pelvic girdle (pelvis inversa). The diaphragm consisted of a thin membranous structure on the right side, but the left half was missing. There was absence of the right suprarenal and the left kidney and their corresponding vessels. The uterus had only one fallopian tube, and there was a persistent cloaca. In addition they found that there was hypoplasia of the thoracic duct, which the authors make responsible for all of the other anomalies on the basis of congenital ascites due to a disturbance of fluid distribution during growth by the atretic diet. The authors give an extensive bibliography of the major congenital malformations, and believe that theirs has never before been reported.

ALFRED J. KOBAK.

CONGENITAL HERNIA AT THE LINEA ALBA. H. R. CHARLTON, Am. J. Obst. & Gynec. **11**:103 (Jan.) 1926.

A six-pound male fetus presented at the umbilicus a grape-fruit shaped tumor, 10 cm. in diameter, which contained intestinal coils, gallbladder and part of the liver. He attempted a plastic operation to reduce the hernia, but the child became cyanotic and died at the end of fifty hours. No postmortem examination was made.

ALFRED J. KOBAK.

REPORT OF A CASE OF DECIDUAL REACTION IN ADENOMYOMA OF RECTOVAGINAL SEPTUM. R. WHITE, Am. J. Obst. & Gynec. **11**:112, 1926.

White reports an interesting tumor of the rectovaginal septum occurring in a multipara who had just become pregnant. The growth, 4 by 2.5 cm., was in the posterior fornix, just at the reflection of the vaginal mucosa from the cervix, and extended in the midline along the axis of the vagina. It was papillomatous and extended into the vaginal submucosa. Microscopically it consisted of a small amount of smooth muscle and an irregular area of glandular tissue which showed a tendency to become cystic and was lined by low cuboidal epithelium, surrounded by a small mass of flat cells which closely resembled uterine mucosa as it appears in the early months of pregnancy. The periglandular stroma was penetrated by large vascular sinuses and in certain areas appeared hemorrhagic. The lesion was regarded as aberrant uterine mucosa undergoing the decidual reaction of pregnancy.

ALFRED J. KOBAK.

REPORT OF A CASE OF MESENTERIC CYST. EDMUND D. CLARK, Am. J. Obst. & Gynec. **11**:238 (Feb.) 1926.

Of the 300 cases of mesenteric cysts including all varieties that have been recorded in the literature, only 10 per cent are connected with the mesentery of the colon. In the case reported by Clark, that of a nullipara aged 51, the chief complaints were a large tumor mass in the abdomen and rapid loss in weight. The tumor mass had been noticed for one year, and began to increase at an alarming rate two months prior to admission. At laparotomy the mass was encased in the mesentery of the transverse colon, was attached to the bowel, but could easily be separated from it. The tumor weighed 3½ pounds (1.6 Kg.) and was 130 mm. in diameter. The surface was well supplied with blood vessels, and there were cysts, 20 mm. in diameter, in the form of nodules on the surface of the mass, the contents of which were a yellowish, gelatinous material mixed with blood. The walls were thin, composed of a cobweb-like,

deeply pink staining connective tissue with poorly staining nuclei. In some of the smaller cysts an endothelial lining was present. The author was unable to determine whether the structure was of embryonic origin, resulted from degenerating lymph glands, or had its origin from dilated lacteals.

ALFRED J. KOBAK.

PEPTIC ULCER OF MECKEL'S DIVERTICULUM. E. STUTZ and P. WORINGER, Ann. Surg. **83**:470 (April) 1926.

Heterotopia of gastric mucosa in Meckel's diverticulum is frequent and often the seat of ulcers. These give rise to intestinal hemorrhages and may perforate into the peritoneal cavity with resultant peritonitis. Such bleeding ulcers occur most frequently in infants and children, and the majority of reported cases have occurred in males. The authors present two cases, one in a boy 4 years old, the other in a boy 11 months old. An ulcer in a Meckel's diverticulum was found in each case to have ruptured and caused localized peritonitis. No histologic studies were made.

N. ENZER.

EXPERIMENTAL HYDRONEPHROSIS. IV. SIMULTANEOUS LIGATION OF THE POSTERIOR BRANCH OF THE RENAL ARTERY AND THE URETER ON THE SAME SIDE. F. HINMAN and A. B. HEDER, Arch. Surg. **12**:830 (April) 1926.

In this study, the rate of development of hydronephrosis following obstruction of the ureter in rabbits was studied, after dividing the posterior branch of the renal artery. The latter causes infarction of one third to one half of the kidney, and the combined procedures result in rapidly developing hydronephrosis and sacculation of the infarcted area. The infarcted tissue offers less resistance to urinary back pressure, which has previously been shown to remain practically unchanged when the posterior branch of the renal artery is divided.

N. ENZER.

INTERSTITIAL GROWTH IN GROWING LONG BONES. S. L. HAAS, Arch. Surg. **12**:887 (April) 1926.

Using the femur and metatarsal bones of young rabbits, the author found that no growth took place between two silver wires or pellets inserted into the diaphysis. The distance between the markers remained constant. He concludes that interstitial proliferation of bony tissue plays no part in the elongation of growing bone.

N. ENZER.

THE DEFENSIVE MECHANISM OF THE PARAMETRIUM DURING PREGNANCY AND LABOR. J. HOFBAUER, Bull. Johns Hopkins Hosp. **38**:255, 1926.

During pregnancy a phagocytic tissue, consisting of monocytes and clasmatocytes, makes its appearance in the base of the broad ligament, and is intensified under the stress of prolonged labor, but particularly by the existence of infection. The development of this tissue from resting-wandering cells and adventitial cells can be demonstrated.

The presence of this phagocytic tissue in the parametrium must be regarded as a prophylactic biologic reaction and as a marked protection against infection. It certainly affords a mechanism for the development of local immunity in a

region abundantly predisposed to infection, and must be of service in doing away with débris and bacteria.

The mode of its production is not yet clear, but it may have important implications in connection with the questions of auto-infection and low cervical section.

The development of lymphoid tissue within the walls of lymphatics in the parametrium must be regarded as an additional defensive mechanism.

AUTHOR'S SUMMARY.

CALCIFICATION OF THE SUPRARENAL GLANDS OF CATS. DAVID MARINE, J. Exper. Med. **43**:495, 1926.

Calcification of the fasicular zone of the cortex has been observed in 64 of 257 cats. It is always calcification and never ossification. It is more common in young animals, and in our experience is associated with distemper. In its severe forms it may be recognized clinically. The symptoms resemble those seen in cats surviving double suprarenalectomy for from two to three weeks. The toxin producing the focal degeneration is clearly a specific one, since attempts to produce such lesions by several types of experimental injury have failed. The sequence of events appears to be similar to that present in other degenerative processes associated with calcification, namely, cell injury and necrosis, deposition of calcium at first as fatty compounds which later change to carbonate and phosphate. It is suggested that this lesion be considered in interpreting experiments in which cats are used.

AUTHOR'S SUMMARY.

HEMOCHROMATOSIS AND CHRONIC POISONING WITH COPPER. F. B. MALLORY, Arch. Int. Med. **37**:336, 1926.

Evidence is slowly but steadily accumulating in favor of the view that chronic poisoning with copper causes the syndrome known under the different names of hemochromatosis, bronzed diabetes and pigment cirrhosis. The author is of the opinion that copper is an exceedingly useful and indispensable metal in many ways, but it should not be employed where it may come in contact with foods or drinks, especially if they contain acids of any sort, because it is so readily dissolved by many of them. This would exclude its use for cooking utensils of any sort, for shakers of cocktails and acid drinks, and for the worms of the condensers in stills. Its use in pipes for drinking water and for hot water heaters is probably without danger.

AUTHOR'S SUMMARY.

NERVE IRRITATION AND AORTIC LESIONS. R. C. SHAW, Quart. J. Med. **74**:203, 1926.

By prolonged stimulation and irritation of the vagus, cervical sympathetic and cardiac depressor nerves, an aortitis of the arch was produced in the majority of rabbits operated on. The lesion followed a definite sequence, beginning with intimal proliferation, which was succeeded by degenerative changes in the media, necrosis and ulcer formation. The methods used were electric stimulation and the production of dense adhesions about the nerves. The article is illustrated by photomicrographs of the lesions.

N. ENZER.

MULTIPLE CHYLANGIECTASES WITH ANGIOMA-LIKE PROLIFERATION IN THE SMALL INTESTINE. F. DANISCH, Centralbl. f. allg. Pathol. u. path. Anat. **36**:385, 1925.

These new growths are of rare occurrence. At necropsy, the mucosa of the jejunum and ileum were found to be hyperemic, and studded with multiple soft yellowish nodules, about the size of peas. When they were opened, a milky fluid escaped. There was none in the large bowel. Microscopically they resembled cavernous hemangiomas consisting of numerous cysts communicating with each other and with the lymph vessels. These growths are classed with the hyperplasias of the lymphatics.

B. R. LOVETT.

APLASTIC LEUKANEMIA. S. M. ZYPKIN, Virchows Arch. f. path. Anat. **258**:600, 1925.

Although Zypkin agrees that the hematologic condition for which von Leube proposed the name of leukanemia is true leukemia which may run a typical or an aleukocythemic course, he retains the name for the report of a fatal case in which the blood contained 245,000 leukocytes, of which 78 per cent were lymphocytes, and 700,000 erythrocytes with no nucleated red corpuscles. The marrow was aplastic. He reaches the general conclusion that the aplastic condition of the bone marrow in any form of anemia is preceded by a hyperplastic stage, and that aplastic anemia is always the end stage of an anemia in which the bone marrow was active at some previous stage.

O. T. SCHULTZ.

MICROSCOPIC STUDY OF VACCINIA AND VARIOLA LESIONS. S. T. SÖRENSEN and E. SÖRENSEN, Virchows Arch. f. path. Anat. **258**:627, 1925.

The authors do not ascribe much value to diagnostic inoculation of the rabbit's cornea, since the specific reaction requires several days for development. They claim that for the clinician familiar with smallpox the diagnosis of the latter should cause no difficulty. The epithelial changes in vaccinia and variola are much alike. Leukocytic infiltration of the vaccinia lesion is not wholly specific, but is due in part to glycerol and other nonspecific constituents of the vaccine. The leukocytes contained gram-negative Prowazek granules. These are not believed to be the actual virus but the carriers of an ultramicroscopic virus. Nuclear changes in the leukocytes lead to the formation of typical Guarnieri bodies.

O. T. SCHULTZ.

LYMPH NODES IN PULMONARY TUBERCULOSIS. G. BAKÁCS, Virchows Arch. f. path. Anat. **258**:646, 1925.

In the study of 100 tuberculous necropsies, Bakács found the regional lymph nodes involved in 98.5 per cent of progressive tuberculosis, in 76.4 per cent of healed tuberculosis, and in 100 per cent of pulmonary tuberculosis in children. He believes that the lung parenchyma is the primary seat of the infection, the hilum and bronchial nodes becoming secondarily involved. From the latter the infection may take a retrograde course downward into the mediastinum and mesenteric nodes and eventually into the intestine, and upward into the supraclavicular and paratracheal nodes and eventually into the tonsils.

O. T. SCHULTZ.

BRUNNER'S GLAND HYPERPLASIAS IN PEPTIC ULCER. N. N. ELANSKY, Virchows Arch. f. path. Anat. **258**:731, 1925.

In twelve cases of chronic gastric and duodenal ulcer, constituting 11 per cent of the material examined, Elansky found adenomatous proliferation of glands of the Brunner type in the walls of the ulcers. He believes that such adenomas arise from embryologically misplaced Brunner's glands which become stimulated to proliferation by the ulcer. Ulcers which contain such adenomatous proliferations are more prone to perforation because of the absence of connective tissue in the glandular areas. Since such Brunner gland adenomas are heterotopic, the author believes that they may become carcinomatous under the influence of the constant irritation of a chronic ulcer.

O. T. SCHULTZ.

AMNIOGENIC MALDEVELOPMENT. H. MATHIS and H. ANGERER, Virchows Arch. f. path. Anat. **258**:757, 1925.

In a teratoid monstrosity the multiple maldevelopments present were ascribed to amniotic adhesions.

O. T. SCHULTZ.

FATTY CHANGE OF INTERSTITIAL TISSUES. W. M. HACKEL, Virchows Arch. f. path. Anat. **258**:771, 1925.

In experimental phosphorus poisoning of rabbits Hackel found slight fatty changes in the capsule, trabeculae and arterioles of the spleen and in the capsule of the liver. Similar changes were not present in the aorta, nor could they be produced in any of the interstitial tissues by chronic intoxication with diphtheria toxin or lactic acid.

O. T. SCHULTZ.

HAIRS IN FECALITHS. R. NEUMANN, Virchows Arch. f. path. Anat. **258**:783, 1925.

Of 1,166 appendixes examined by Neumann, 325 (28 per cent) contained fecaliths. One hundred and forty-five (42 per cent) of the latter contained hairs, which the author believes responsible for the formation of the fecaliths. In 80 per cent the hair was human. In only one case were pig's bristles found, supposedly derived from the toothbrush.

O. T. SCHULTZ.

LOOSE BODIES OF THE KNEE-JOINT. K. VON DITTRICH, Virchows Arch. f. path. Anat. **258**:795, 1925.

From a histologic study of an early loose body of the knee joint and of a second similar lesion which had not yet become separated, von Dittrich concludes that there is no true inflammatory reaction and that the term osteochondritis dissecans proposed by Koenig is not apropos. The changes noted consisted of hemorrhage, edema, degeneration and necrobiosis, which lead to separation of the tissue and formation of the loose body. These changes were believed to be the result of trauma. The latter need not be an injury in the usual sense, but may be only the traction exerted by a ligament at or near its insertion. The author accepts the term proposed by Kappis, "osteochondrolysis," which he modifies by the adjective, "traumatica."

O. T. SCHULTZ.

ACUTE MYOCARDITIS DUE TO IODINE. K. TAKANE, Virchows Arch. f. path. Anat. **259**:1, 1926.

In continuation of some previously published work in which it was found that organic and inorganic iodine compounds, including thyroid preparations, caused acute myocarditis when administered to white rats, Takane attempts to find the cause for the effect of iodine compounds on the myocardium. He concludes that lactic acid liberated by the heart muscle, which contains only small amounts of salts or protein which will bind the lactic acid, frees the iodine from its compounds and that the free iodine then acts harmfully on the myocardium. This harmful action manifests itself only in the heart, other organs and tissues containing sufficient substances which combine with lactic acid to prevent the liberation of iodine.

O. T. SCHULTZ.

THE SECRETING CELLS OF THE THYROID. J. M. LASOWSKY, Virchows Arch. f. path. Anat. **259**:68, 1926.

Lasowsky claims that in the early stage of the regenerative hyperplastic process which follows experimental removal of part of the thyroid the colloid is formed by the destruction of the follicular epithelium, forming the metanuclear colloid of Wail. In the later stages of the process the colloid, metaplasma colloid of Wail, is formed as a true secretion process of the epithelial cells. The chief cells of Langendorff are follicular epithelia which have become exhausted by secretory activity. Interfollicular epithelial islands, which are numerous in young animals, may form true follicles by the development of secretory activity of the cells or they may form interfollicular colloid by necrobiosis.

O. T. SCHULTZ.

METAPLASIA OF BRONCHIAL EPITHELIUM. E. BRACK, Virchows Arch. f. path. Anat. **259**:79, 1926.

The apparent increase in the frequency of carcinoma of the lung led Brack to make a study of the occurrence of metaplasia in the bronchial and alveolar epithelium of the lung. True metaplasia, by which the bronchial epithelium is transformed from the cylindrical to the squamous type, was found to occur fairly frequently in localized, chronic inflammatory processes, especially in children. Compression of bronchial and alveolar epithelium by interstitial fibrosis Brack terms pseudometaplasia.

O. T. SCHULTZ.

EPITHELIAL METAPLASIA OF EPIDIDYMIS. T. KONSCHEGG, Virchows Arch. f. path. Anat. **259**:89, 1926.

Squamous cell metaplasia of the cylindrical cell epithelium of a chronically inflamed epididymis is reported by Konschegg. He believes that the aberrant epithelium arose during the regenerative stage of the inflammatory process from indifferent basal cells of Krompecher.

O. T. SCHULTZ.

ENDOMETRIOID HETEROTOPIAS. K. O. POLSTER, Virchows Arch. f. path. Anat. **259**:96, 1926.

To the rapidly growing recent literature relating to endometrioid heterotopias, Polster adds a discussion based on seven extra-uterine and six intrauterine examples of the condition. In the first group there were two of the

ovary, one of the tube, two of the sigmoid region, one of the round ligament and one of an abdominal scar. He believes that a variety of factors may be concerned in the formation of these heterotopias, but gives scant attention to embryonic misplacement. Regenerating peritoneal mesothelium may produce structures which resemble uterine glands, but the derivation of extra-uterine endometrioid heterotopias from such regenerating mesothelium has not been established. Indifferent serosal mesothelium, which retains some of the multiple potentialities of the celomic epithelium, might produce structures of endometrial type. Transplantation and implantation of uterine endometrium is granted to be theoretically possible and to have been proved experimentally, but Polster doubts that the endometrium exfoliated during menstruation is capable of implanting itself and of undergoing progressive growth. In endometriosis and adenomyoma of the uterus, penetration of the myometrium by regenerating endometrium, especially after childbirth, may be a factor, since the uterine form of the condition is more frequent in older women who have borne children, whereas the extra-uterine examples usually occur in younger or in sterile women. Halban's theory, that endometrium which has penetrated the myometrium may enter the lymphatics and establish itself at some distance, is held to be untenable.

O. T. Schultz.

Secondary Follicles of Lymph Nodes. P. Heilmann, Virchows Arch. f. path. Anat. **259**:160, 1926.

The pale staining centers of lymphoid follicles, termed by Flemming germinal centers under the belief that they are the site of formation of lymphocytes, are termed by Heilmann, in agreement with Hellman, secondary follicles. They are composed of hyperplastic reticulo-endothelial cells which are phagocytic of damaged lymphocytes, the center, as a whole, functioning as an antibody-forming organ. The centers develop only after birth as the reaction to stimuli acting on the lymphoid tissues, and are therefore to be looked on as pathologic, although the stimulus which leads to their formation may be a physiologic one. In this case the large cells of the center show no regressive changes. If the stimulus is excessive or abnormal, the reaction centers become pathologic, the cells showing evidences of degeneration, necrobiosis and replacement by stroma. This conception is of considerable interest when applied to status lymphaticus, which is not considered a true lymphoid hyperplasia. In status lymphaticus with its marked formation of secondary follicles throughout the lymphoid tissues of the body, there occur destruction and disappearance of lymphocytes with hyperplasia of the reticulo-endothelial lymphoid immunity organs compensatory to exogenous or endogenous toxins. Prolonged or excessive action of the latter leads to exhaustion of the reaction centers and to their replacement by connective tissue. The small lymphoid follicles without "germinal centers," which occur in inanition and cachexia, indicate a loss of reactivity by, and of the protective mechanism of, the lymphoid tissues.

O. T. Schultz.

Concerning the Pathogenesis of Local Selective Brain Changes. W. Spielmeyer, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:756, 1925.

Spielmeyer discusses the predilection of disease processes for certain portions of the brain and brings out the difficulties for the pathologist, particularly because the end result of inflammatory, circulatory and degenerative diseases may be identical. He believes there is much to the Vogts' conception that

pathoklisis or local susceptibility of portions of the brain is due to a different inherent physicochemical constitution of the various cerebral structures. In typhoid fever, for example, Spielmeyer has shown a pure isolated degenerative lesion of the dentate nucleus with glial replacement without dependence on the vascular supply. Similarly in typhus he has shown isolated changes of the Purkinje cells of the cerebellum. There is no other explanation for the localization of these lesions than that of the Vogts. It must be realized that there is only negative evidence for this theory.

The author finds Ammon's horn very susceptible to all toxins, with changes often entirely limited to the juxtaventricular portion. In cases of tuberculous meningitis with peri-arteritis and endarteritis, in general paralysis and senile dementia, he finds this area involved. Since the basis of the changes in the reported cases was vascular, and identical areas were affected, Spielmeyer believes that the predilection of Ammon's horn is due to its vascular supply. He has reported Ammon's horn lesions in epilepsy and now suggests that they may be due to vascular spasms in this region.

In carbon monoxide poisoning the anterior portion of the pallidum is usually softened. Spielmeyer believes that this area is so regularly necrotic because of the peculiar backward flow of its subserving vessels. A case is described in which three hours after poisoning vasodilation and hyperemia were present in the anterior pallidum. Spielmeyer concludes that the site of a lesion is dependent on a combination of (1) tissue affinity or the "system factor," (2) vascular supply or the "vasal factor."

ROY GRINKER.

THE FORMATION OF CORPORA AMYLACEA IN THE BRAIN IN CONNECTION WITH CRYSTALLIZATION PROCESSES IN THE CENTRAL NERVOUS SYSTEM. L. J. OMOROKOW, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:109, 1926.

The theories as to the formation of amyloid bodies in the brain are as follows: from glia cells and nuclei; from axis cylinders and myelin sheaths or each separately; lymphogenous, a precipitate of tissue juices; hematogenous, postmortem changes. Amyloid bodies are insoluble in water, even on boiling, in alcohol, ether, chloroform, benzine, and dilute acids. Acetic acid makes them unstainable with iodine. Strong alkali breaks them up and slowly dissolves them. They stain violet with iodine, and with the addition of sulphuric acid become dark red. They stain with Best's glycogen stain. The amyloid bodies are spherical with regular concentric layers and radial markings. They contain a crystalloid center and are doubly refractile.

The author studied several cases of corpora amylacea and concludes that they are chemically not the same throughout their development. The characteristic reactions to iodine and sulphuric acid occur only when they are fully formed and free in the tissue. They developed similarly from the substance of ganglion cells and nerve fibers. There is first a severe degeneration of the nerve cells with a clumping of the Nissl bodies and the formation of basophilic granules in the protoplasm. These granules coalesce into droplets of myelin-like substances which are metachromatic and stain dark blue with hematoxylin. A physical change then takes place in the amorphous mass; definite layers are formed, and a spherical shape is assumed. The ganglion cells during this process may undergo neuronophagia by glia. The glia subsequently degenerate, leaving the amyloid bodies free in the tissue.

ROY GRINKER.

THE BLOOD PICTURE AND DIGESTIVE LEUKOCYTOSIS IN DIFFERENT CONSTITUTIONAL ANOMALIES. A. F. TUR, Jahrb. f. Kinderh. **111**:29, 1925.

Tur found that normal children show a slight decrease in leukocytes one hour after a meal, followed by a greater increase, 15 to 45 per cent, three hours after. The increase was chiefly in the neutrophils. Children of lymphatic-hypoplastic constitution had a slight increase in total white cells with lymphocytosis one hour after eating, and an increase in neutrophils, as in normal children, three hours after. The asthenic children varied, one-third showing a leukopenia in one hour followed by a leukocytosis, and two-thirds having only the leukocytosis. A small group of children of neuro-arthritic type showed leukocytosis one hour after the meal, and leukopenia three hours after. In none was there marked shifting of Arneth's formula to the left, so that the leukocytosis is probably one of distribution, depending possibly on differences in the tonus of the vegetative nervous system.

B. R. LOVETT.

THE PATHOLOGY OF ENCEPHALITIC PARKINSONISMUS. L. B. HOHMAN, Wiener Neurol. Inst. Arb. **27**:1, 1925.

Eleven cases were studied and generalized lipodystrophia found in all, most marked in the olive and dentate nuclei. There were severe ganglion cell changes in areas without inflammatory reactions and in other areas with lymphocytic and plasma cell accumulations. The cell changes were believed to result from inflammation and not from degeneration. Uniformly the substantia nigra was degenerated, with acute swelling, disintegration of the cells and loss of pigment. There was a discontinuous axonal degeneration and swelling, especially about the vessels. The substantia nigra, pallidum, striatum, dentate nucleus and cortex were affected in the order of severity. The author believes that the process is a chronic progressive inflammation complicated by diffuse fatty changes of the cells. The latent period may be long between the initial infection and the sequelae, but the original disease persists. Because the substantia nigra is most severely attacked in these hypertonic states, it is presumed to be most concerned with tonus.

ROY GRINKER.

SALIVARY CONCREMENTS. CARL NAESLUND, Acta path. et microbiol. Scandinav. **2**:244, 1925.

Cultural and experimental investigations lead to the conclusion that the nucleus for the formation of salivary concrements consists of actinomycelial masses.

GLIA AND THE CELL. S. T. BOK, Nederl. Tijdschr. v. Geneesk. **1**:414, 1926.

The alleged cell represents the range of influence of a nucleus lying in a mass protoplasm which is connected directly with the protoplasm about other nuclei. As the glia becomes visible in stained preparations, the protoplasm is changed both chemically and physically.

CYSTS. TAKAYOSHI SUZUKI, Acta dermat. [Japanese] **7**:12, 1926.

An instance of cystic kidneys in a rabbit was studied. The cysts arose from Boman's capsule as well as from the tubules in the medulla. There was no epithelial proliferation of the cyst lining and no inflammatory lesions in the medulla, the cysts depending clearly on a congenital disturbance of development in the kidney.

Pathologic Chemistry

URIC ACID AND CREATININ IN THE URINE OF INFANTS. O. S. ROUGICHITCH, Am. J. Dis. Child. **31**:504, 1926.

In twenty-two male infants on purin-free diets, the uric acid output for twenty-four hours ranged from 14 to 25 mg. per kilogram of body weight, and in the individual was practically constant. There was no distinct relation to the total nitrogen in the urine, or to the nutritional state, except for one very high test in a child with rickets.

The creatinin, averaging 10 to 15 mg. per kilogram of body weight was highest in the poorly nourished, and also in one child with frequent convulsions. In general there was no relation between the creatinin content and the muscle tonus or the amount of sleep.

E. B. PERRY.

SOME OBSERVATIONS ON THE EXTRACTION OF THE VITAMIN B FROM WHEAT GERM. E. V. MCCOLLUM and H. D. KRUSE, Am. J. Hyg. **6**:197, 1926.

With 95 per cent alcohol containing 1 per cent gallic or tannic acid satisfactory results were obtained in extracting vitamin B from wheat germ. Similar experiments with other acids yielded only fair or negative results. The extracts were tested by the method described by McCollum and Simmonds (*J. Biol. Chem.* **33**:55, 1918).

A STUDY OF BLOOD DIASTASES IN DEPANCREATIZED DOGS. J. MARKOWITZ and H. B. HOUGH, Am. J. Physiol. **75**:571 (Feb.) 1926.

In completely and partially depancreatized dogs there occurs a great decrease in blood diastase, promptly in the former, delayed in the latter. This primary fall is compensated in the course of some months in animals kept alive with insulin, by a restoration to normal. The blood diastase is little affected by the injection of insulin, and that variably. No evidence was obtained pointing to the value of blood diastase determinations in clinical diabetes.

H. E. EGGERS.

BLOOD CHOLESTEROL FINDINGS IN SYPHILIS AND IN OTHER SKIN DISEASES. ISADORE ROSEN and FRANCES KRASNOW, Arch. Dermat. & Syph. **13**:506 (April) 1926.

The cholesterol was extracted by a modification of the method of Myers and Wardell (*J. Biol. Chem.* **38**:147, 1918), which is believed to give accurate results. The details of the process will be described later. The blood cholesterol was low in all patients examined that suffered from untreated primary syphilis. After treatment the content increased. There was no indication of any relation between the cholesterol content of the blood and the outcome of the Wassermann test.

SIGNIFICANCE OF BLOOD CHEMICAL CHANGES IN PERTUSSIS. JOSEPH C. REGAN and ALEXANDER TOLSTOUHOV, J. A. M. A. **86**:1616, 1926.

There occurs in pertussis an uncompensated acidosis, which is intimately connected with the pathogenesis of the paroxysms. If the acid base unbalance is corrected, the clinical symptoms are quickly ameliorated, and the organism returns to normal.

A Modified Methyl Orange Indicator Suitable for Use with Artificial Light. A. J. Salle, J. Infect. Dis. **38**:293, 1926.

A modified methyl orange indicator is described consisting of methyl orange, acid green and acid blue which may be used with artificial as well as with natural light for titrations and for the colorimetric determination of hydrogen ions having a range between p_H 2.6-4.2.

Author's Summary.

The Chemical Configuration of Thyroxin and Its Mode of Action in the Tissues. E. C. Kendall, Proc. Am. Soc. Biol. Chem., J. Biol. Chem. **67**:3, 1926.

Thyroxin, epinephrine, and glutathione are members of a group of substances which furnish to the animal organism an active chemical grouping. They establish the intensity of the oxidation reduction process occurring within the cells, and produce a poising effect, maintaining the intensity of oxidation and reduction within narrow limits. These substances are most active in a state of intermediate oxidation, when they may have the properties of free radicals.

Arthur Locke.

The Inorganic Phosphorus and Calcium of the Blood in Nephritis. H. W. Schmitz, E. L. Rohdenburg and V. C. Myers, Arch. Int. Med. **37**:233, 1926.

A relatively high percentage of cases of chronic interstitial nephritis with muscular twitchings or convulsions show values for the calcium of the blood serum below 7 mg. per hundred cubic centimeters. There is no uniform inverse relationship between the level of the inorganic phosphorus of the serum and the calcium in different cases. In other words, the retention of phosphorus has a greater influence in some cases than in others. However, in individual cases one notes a gradual fall in the calcium with a rise in the inorganic phosphorus. Low figures for the carbon dioxide capacity of the plasma may be present in the absence of high figures for the inorganic phosphorus, but cases showing high figures for the inorganic phosphorus are almost invariably accompanied by low figures for the carbon dioxide capacity of the plasma. Here the few observations recorded for the p_H indicate that the acidosis is generally of the uncompensated variety. There is little doubt about the reliability of inorganic phosphorus retention as a prognostic sign in chronic nephritis, but the creatinin is equally reliable and the retention appears to occur a little earlier than is the case with the inorganic phosphorus.

S. A. Levinson.

Studies on Biochemical Differences Between (+) and (—) Sexes in Mucors. 2. A Preliminary Report on the Manoilov Reaction and Other Tests. Sophia Satina and A. F. Blakeslee, Proc. Nat. Acad. Sc. **12**:191, 1926.

The opposite sexes of *Mucors*, designated (+) and (—) because they lack constant morphologic differences by which they may be recognized as male and female, were subjected in pairs to many biochemical tests. Races were found to differ biochemically even when of the same sex, but comparisons of the two sexes show that the (+) race has an average greater catalase and peroxidase production, reducing power, and Manoilov reaction which corresponds to the female in higher plants and animals.

Ethel B. Perry.

HAEMOCHROMOGEN CRYSTAL TEST FOR BLOOD. D. J. A. KERR and V. H. MASON, Brit. M. J. **1**:134, 1926.

Takayama's solution 2, containing equal parts of sodium hydroxide (10 per cent), pyridine, and saturated solution of grape sugar, in distilled water (2½ parts) yielded characteristic salmon-pink, shallow rhomboidal hemochromogen crystals with various specimens of blood, including those 45 years old, mixed with rust, washed with hot water, or otherwise heated to 100 or even 150 C. The tests for hemin crystals, in which the Sutherland method was found preferable, were in some instances negative, and were therefore judged less sensitive and also more easily inhibited by overheating than the hemochromogen crystal test which may be done either with or without heat. The spectroscopic tests of the resulting pyridine compounds of hemochromogen are uniform and afford confirmation of the initial crystal study.

ETHEL B. PERRY.

THE BLOOD-FATS IN DIABETES MELLITUS IN RELATION TO TREATMENT. A. C. WHITE, Quart. J. Med. **74**:159 (Jan.) 1926.

The authors studied the blood-fat level in thirteen diabetic patients and found that it was invariably lowered by insulin, especially when it had reached a high level. They considered that this was due to the improved carbohydrate metabolism and that therefore the insulin effect on blood fat is an indirect one. The use of the blood-fat level as a prognostic sign requires more investigation on a larger series of patients. The age and the weight of the patient influence the results very little. It is important in studying the blood-fat to study closely the state of nutrition for some time before the blood is taken for examination, and they recommend a longer period of fasting, favoring the fourteen hour period as preferable to the twelve hour period. A review of the literature is given, and a bibliography is appended.

N. ENZER.

PHOSPHORUS POISONING AND LIVER ENZYMES. M. STAEMMLER, Virchows Arch. f. path. Anat. **259**:326, 1926.

In continuation of a previous study of the ferment activity of the liver in experimental phosphorus poisoning, Staemmler finds that phosphorus in high dilution in vitro inhibits the diastatic activity of normal liver tissue, but in vivo only slight inhibiting action could be detected. He concludes that the disappearance of glycogen from the liver in phosphorus poisoning is not due to increased destruction of glycogen through the activity of diastatic enzymes, but is probably due to decreased glycogen synthesis caused by enzyme injury.

O. T. SCHULTZ.

IS THE SURFACE OF BLOOD SERUM A CONSTANT QUANTITY? K. BECHMANN, Klin. Wchnschr. **5**:215, 1926.

Edematous conditions are accompanied by large fluctuations in the value of the static surface tension of the blood serum.

ARTHUR LOCKE.

THE POLYPHASE ACTION OF THE HORMONES. V. M. KOGAN, M. J. KAMENEW and N. B. MANTZ, Klin. Wchnschr. **5**:221, 1926.

The action of a hormone on an organ system is dependent on all of the influencing conditions, and the qualitative differences in the action of hormones on different organs are due to differences in these conditions.

ARTHUR LOCKE.

FURTHER EXPERIENCE WITH MY CHEMICAL BLOOD REACTION FOR THE IDENTIFICATION OF SEX IN MAN AND ANIMALS AND BY THE CHLOROPHYLL OF PLANTS. E. O. MANOILOFF, München. med. Wchnschr. **71**:174, 1924.

Of the three modifications of the author's earlier method for the differentiation of male and female blood, the third gave the highest percentage of correct identifications—86 to 96 per cent. Five reagents were used: (1) 1 per cent aqueous solution Papayotin (Merck), filtered; (2) 1 per cent alcoholic solution Dahliafarbe (Grübler) or methyl violet, 1912, filtered; (3) 1 per cent aqueous solution of potassium permanganate; (4) 40 per cent hydrochloric acid (40 cc. conc. HCl—60 cc. H_2O); (5) 2 per cent thyocyanamine (very soluble in cold water, warm and filter). To 3 cc. of unheated erythrocyte suspension add: 10 drops of (1) (1 min., mix—*not shake*); 3 drops of (2) (do not shake); 10 drops of (3) (same); 3 drops of (4), shake, and 5 drops of (5) and shake. The male blood becomes colored and the female blood does not. Only hypothetical explanations could be offered. Something in the female blood seems to prevent the formation of a leukobase; the addition of sodium fluoride will change the reaction to a positive color production. The reaction may depend on an oxidation process, or perhaps the electrostatic charge has an influence.

ETHEL B. PERRY.

STUDIES ON THE FAT-CHOLESTEROL CONTENTS OF THE BLOOD OF RABBITS WITH EXPERIMENTAL NEPHRITIS. H. J. BING, H. HECKSCHER and J. JESSEN, Acta path. et microbiol. Scandinav. **2**:234, 1925.

The nephritis was produced with uranyl acetate, potassium chromate and phosphorus in olive oil. The results indicate "a connection between certain protein—and the 'fat' colloids of the blood" in the decrease of the protein concentration may produce an increase of fat and vice-versa.

Microbiology and Parasitology

ERYTHEMA INFECTIOSUM. THEODORE P. HERRICK, Am. J. Dis. Child. **31**:486, 1926.

A series of seventy-four personally observed cases of erythema infectiosum is presented, and all the evidence in these cases indicates that the disease is a distinct entity, is infectious, and results in the establishment of a specific immunity.

The distinguishing features of the disease are its occurrence in epidemics, the lack of constitutional symptoms, the lack of any features distinctive of the other exanthems, the long course and characteristic progression of the rash, its evanescence at all stages, and particularly the irregular but brilliant outlines seen on the arms and legs in the third stage and in the recurrences.

AUTHOR'S SUMMARY.

OCCURRENCE OF THROAT INFECTIONS WITH STREPTOCOCCUS SCARLATINAE WITHOUT A RASH. FRANKLIN A. STEVENS and A. R. DOCHEZ, J. A. M. A. **86**:1109, 1926.

Scarlatinal infection of the throat may occur without a rash.

This type of infection may occur in individuals showing negative skin reactions to scarlatinal toxin.

The Dick test is not a reliable index of immunity to such throat infections with *Streptococcus scarlatinae*.

In the series of cases observed, agglutination reactions with scarlatinal serum and toxin production are closely parallel.

There is no antigenic relationship between strains of hemolytic streptococci from acute streptococcus pharyngitis.

AUTHORS' SUMMARY.

THE NASAL PASSAGES IN LOBAR PNEUMONIA. A. R. FELTY and C. A. HEATLEY, J. A. M. A. **86**:1195, 1926.

In a series of sixteen cases of lobar pneumonia, pneumococci of corresponding type to those found in the sputum were isolated from the middle fossae of the nose in every case.

The nasal passages in fifteen of the sixteen cases were examined with the nasopharyngoscope; of these, all showed hyperemia of the mucous membranes, and six had signs of acute suppurative sinusitis. In eight cases, anteroposterior roentgenograms of the sinuses were made; in seven cases, clouding of one or more of the sinuses was observed.

In this small series of cases, acute pneumococcal sinusitis was a frequent accompaniment of lobar pneumonia.

AUTHORS' SUMMARY.

THE PREVALENCE OF CARRIERS AMONG RECOVERED TYPHOID PATIENTS. CHARLES N. LEACH, SOPHIE A. DEHLER and LEON C. HAVENS, Am. J. Pub. Health **16**:391, 1926.

In the examination of 156 individuals who had recovered from typhoid fever within from six months to two years, 10.3 per cent were found to be typhoid carriers. These results show a percentage distinctly higher than those reported by previous investigators in the United States.

AUTHORS' SUMMARY.

TYPHOID ABSCESS OF THE BREAST. P. O. SNOKE and J. L. GOFORTH, Am. J. Med. Sc. **171**:555, 1926.

A case is reported of typhoid abscess of the breast occurring in a young negress one year after lactation. It was preceded by three postlactation masses; these perhaps were periductal adenofibromas, which may have afforded foci for the localization of the typhoid bacilli. Enlarged masses in the axillary fold proved to be periductal adenofibromas, presumably of misplaced mammary tissue. The differential diagnosis from tuberculosis of neoplasm could not be made before the breast was amputated.

AUTHORS' SUMMARY.

SYPHILITIC MYOCARDITIS IN THE RABBIT. WADE H. BROWN and LOUISE PEARCE, J. Exper. Med. **43**:501, 1926.

In the course of routine postmortem examinations of rabbits infected with *Spirochaeta pallida*, six cases of pronounced granulomatous myocarditis were encountered. Spirochetes were not demonstrated in the lesions, but the clinical history and the gross and microscopic appearance of the lesions seemed to warrant a diagnosis of syphilitic myocarditis. The lesions measured 1 cm. or more in diameter, and histologically were practically identical with those described by Warthin in cases of syphilitic myocarditis in man.

These are the first cases of syphilitic myocarditis or of visceral syphilis in the rabbit that have been reported.

AUTHORS' SUMMARY.

CULTIVATION OF RICKETTSIA-LIKE MICRO-ORGANISMS FROM THE ROCKY MOUNTAIN SPOTTED FEVER TICK, DERMACENTOR ANDERSONI. HIDEYO NOGUCHI, J. Exper. Med. **43**:515, 1926.

A systematic study of seventy-four ticks, the infectivity or noninfectivity of which was determined by biting experiments, inoculation of emulsions and specific immunity tests, showed the presence in some instances of several types of micro-organisms morphologically resembling the inciting micro-organism of spotted fever. The most frequently isolated was *B. rickettsiformis,* n. sp.; those less commonly encountered were *B. pseudoxerosis,* n. sp., and *B. equidistans,* n. sp. These organisms are nonpathogenic for the guinea-pig, rabbit, and *Macacus rhesus.* In morphologic features they resemble the forms found in smears and sections of the ticks; yet their presence had no relation to infectivity. Immunologically they are not related to the spotted fever virus. All three are pleomorphic under cultural conditions, and the question arises whether or not the minute nonpathogenic *Rickettsia* forms and the somewhat coarser symbionts found in *Dermacentor andersoni* are morphologic variations due to variations in nutrition, oxygen tension, tissue reactions, etc., in the different tissues and cells in which the organisms are embedded. At all events, the differentiation of the nonpathogenic Rickettsia-like organisms from *Dermacentroxenus rickettsi* is extremely difficult. In definitely infective ticks of the present study intranuclear forms were not constant.

A point of special interest is that these nonpathogenic micro-organisms from ticks grow best at room temperature, in this respect resembling culturally certain flagellates inhabiting the alimentary tract of insects. The difficulty of obtaining initial growth on artificial mediums and the gradual adaptation to less specialized mediums are other notable characteristics of these organisms. The possibility that *B. rickettsiformis* is a nonpathogenic phase of the spotted fever organism, comparable with the avirulent flagellate culture forms of *Leishmania,* seems remote in view of the negative immunologic findings.

Hereditary transmission of *B. rickettsiformis* is clearly indicated by its presence in large numbers in ovaries and egg cells, a characteristic also of the spotted fever organism and of other insect-borne rickettsias.

AUTHOR'S SUMMARY.

EPIDEMIOLOGICAL STUDIES ON RESPIRATORY INFECTIONS OF THE RABBIT. VII. PNEUMONIAS ASSOCIATED WITH BACTERIUM LEPISEPTICUM. LESLIE T. WEBSTER, J. Exper. Med. **43**:555, 1926.

Four general types of spontaneous pneumonia, associated with strains of *Bact. lepisepticum* similar in biology and virulence, are described: (1) an acute, diffuse form, with subpleural and perivascular orientation of the exudate, (2) lobar, (3) pleural pneumonia, and (4) abscess pneumonia.

The acute, diffuse, lobar and pleural pneumonias may be induced experimentally by intranasal instillation of a virulent strain of *Bact. lepisepticum.*

These same types occur when the organisms are inoculated intravenously, intratesticularly and subcutaneously.

Intrabronchial insufflation of the organisms brings about infection in less than half of the animals. When effective, a sharply circumscribed, peribronchial lesion is found at the base of the lung, which spreads peripherally by direct extension, and generally by invasion of the blood stream.

It is concluded that differences in the types of pneumonia following infec-

tion with similar strains of *Bact. lepisepticum* depend on the resistance of the animal, and that the usual portal of entry of this organism into the lungs, in cases of acute and lobar pneumonia, is by way of the blood stream.

AUTHOR'S SUMMARY.

STUDIES IN BACTERIAL METABOLISM. LXXVI. NATURE OF THE SOLUBLE PROTEOLYTIC ENZYME OF BACILLUS PROTEUS. ARTHUR ISAAC KENDALL and HAZEL R. KEITH, J. Infect. Dis. **38**:193, 1926.

The soluble bacteria-free proteolytic enzyme of *Bacillus proteus* effects a rapid change in the gelatin molecule. The nature and extent of this change is of the tryptic rather than of the peptic type. The rate and course of action of the proteus enzyme equals, or even exceeds, that of commercial trypsin under parallel conditions, so far as they are reproducable in these experiments.

AUTHORS' SUMMARY.

CHEMISTRY OF THE INTESTINAL FLORA OF NURSLINGS. STUDIES IN BACTERIAL METABOLISM. LXXVII. ARTHUR ISAAC KENDALL, ALEXANDER ALFRED DAY and ARTHUR WILLIAM WALKER, J. Infect. Dis. **38**:200, 1926.

The nitrogenous metabolism of the mixed intestinal flora of a series of twelve normal nurslings shows that the nitrogenous changes induced by the microbes are relatively small. Proteolysis of bacterial origin is minimal.

The striking change induced by the mixed flora is a pronounced fermentation of utilizable carbohydrates, particularly glucose and lactose. In these mediums, there is a rapid and intense formation of acid, with almost no indication of nitrogenous change in the constituents of the medium other than those ultimately associated with the anabolic phase of bacterial activity.

This pronounced fermentation (principally lactic) is characteristic of the chemistry of the combined fecal bacteria of nurslings.

AUTHORS' SUMMARY.

CHEMISTRY OF THE INTESTINAL BACTERIA OF ARTIFICIALLY FED INFANTS. STUDIES IN BACTERIAL METABOLISM. LXXVIII. A. I. KENDALL, A. A. DAY and A. W. WALKER, J. Infect. Dis. **38**:205, 1926.

The composite changes induced in suitable cultural mediums by the intestinal floras of artificially fed infants reported herewith are representative for the small series studied. They do not necessarily typify those that might be encountered in other similar groups. Hence, they are to be considered as suggestive rather than definitive.

The outstanding feature centers around the striking difference between the nitrogenous metabolism of the floras in plain sugar-free mediums and in carbohydrate-enriched mediums, respectively.

In the former, the nitrogenous constituents are rather profoundly degraded, and the microbes utilize the products of degradation — polypeptids apparently — for energy, as well as for structure.

The addition of utilizable carbohydrate to such mediums, prior to the infection with the intestinal organisms, shifts the catabolism of the bacteria from protein to carbohydrate. This is indicated both by the slight changes detectable in the nitrogenous constituents of the carbohydrate-containing mediums, and also by the rapid accumulation of acid. Stated differently, the

intestinal floras of artificially fed children induce putrefactive changes in sugar-free mediums and fermentative changes in the same mediums to which carbohydrates have been added.

It must be remembered that the effects of supplying utilizable sugars to the intestinal organisms which are so strikingly brought out in the tables, are those induced in test tubes, outside the intestinal environment. It is probable, however, that parallel changes would take place within the alimentary canal, provided utilizable carbohydrate could be kept continuously at levels of the intestinal tract where proteolysis would otherwise take place.

AUTHORS' SUMMARY.

CHEMISTRY OF THE INTESTINAL FLORA OF NORMAL ADULTS. STUDIES IN BACTERIAL METABOLISM. LXXIX. A. I. KENDALL, A. A. DAY and A. W. WALKER, J. Infect. Dis. **38**:211, 1926.

The general results obtained from the metabolic study of these fairly representative intestinal floras from normal adults is a chemical picture of rather unexpected uniformity so far as the nitrogenous changes induced by the microbes are concerned.

This picture is one of moderate proteolysis in mediums containing no utilizable carbohydrate, and a suppression of this proteolysis nearly to the vanishing point when utilizable carbohydrates are added.

These changes are not unlike those induced by pure cultures of colon bacilli and *Bacillus mesentericus* grown under parallel anaerobic conditions, but it must not be inferred that these bacilli alone are concerned; both stained preparations prepared from the several cultures and actual isolations show a considerable variety of forms and types, gram-negative organisms predominating.

Nor is this moderate proteolysis, occurring characteristically in the sugar-free mediums, one free from aromatic products of putrefaction. Indol was present in each plain broth culture after the third day of incubation, and earlier in some. Of theoretical importance, however, is the complete absence of indol in glucose, starch and milk cultures, with the exception of one starch culture (number 2) that had an unusual amount of polypeptid nitrogen.

One of the potentially useful facts gleaned from these observations is the striking effect of diet on the nitrogenous metabolism of these normal adult bacteria: utilizable carbohydrate, as long as it is continuously available, reduces or suppresses aromatic putrefactive products practically to the vanishing point.

Another feature which must be regarded as of tentative significance only in view of the small number of observations, is the low proteolytic change in plain broth cultures, which contrasts strikingly with the marked proteolysis in those persons whose intestinal flora contains a distinct overgrowth of gas bacilli, *Bacillus aerogenes-capsulatus*.

AUTHORS' SUMMARY.

CHEMISTRY OF THE INTESTINAL FLORA OF MAN CONTAINING ABNORMAL NUMBERS OF GAS BACILLI. STUDIES IN BACTERIAL METABOLISM. LXXX. A. I. KENDALL, A. A. DAY and A. W. WALKER, J. Infect. Dis. **38**:217, 1926.

The outstanding characteristic in the metabolism of the intestinal flora of persons having an overgrowth of gas bacilli in their alimentary tracts is seen in mediums containing no utilizable carbohydrate, as gelatin broth. Here there is considerable and rapid degradation of the protein. This is accompanied by

unusually extensive deamination, resulting in the accumulation of much ammonia in the culture.

In carbohydrate-containing mediums, and especially in milk, there is a complete, or nearly complete, suppression of this proteolysis, and of deamination as well.

It must be emphasized that this characteristic reaction is quantitative rather than qualitative in its significance, and a much larger series must be available before unassailable conclusions can be drawn.

AUTHORS' SUMMARY.

THE TREATMENT OF HUMAN TRYPANOSOME INFECTION BY TRYPARSAMIDE. J. LAIGRET, Ann. de l'Inst. Pasteur **40**:173, 1926.

Ninty-five patients with sleeping sickness in the second stage were treated with tryparsamide with results superior to those obtained by the use of atoxyl. Intravenous or intramuscular inoculations were given. Subcutaneous inoculations give rise to extensive abscesses. Carefully graded small doses are indicated in advanced stages of the infection to minimize the danger of visual disturbances.

G. B. RHODES.

EXPERIMENTAL TYPHOID INFECTIONS IN GUINEA-PIGS. M. GORY and JEAN DALSACE, Ann. de l'Inst. Pasteur **40**:194, 1926.

A constant clinical and pathologic process similar to that observed in human typhoid infections was produced in guinea-pigs by subconjunctival inoculations of small amounts of cultures of *B. typhosus*, using strains which were controlled as to virulence.

Positive blood cultures were not obtained after the third day and agglutinins were not constant, never occurring before the seventh day. Cholecystitis was the characteristic lesion produced. Immunity was established after a nonfatal primary infection.

G. B. RHODES.

CANINE TUBERCULOSIS WITH A NONCULTURABLE VIRUS. K. LANKEN, Beitr. z. Klin. Tuberk. **62**:709, 1926.

In a dog who died during an operation, hard and swollen mesenteric glands were found, which contained a clear fluid with an enormous number of acid-fast rods. These bacilli failed to grow on various mediums. Passing the diseased organs through a series of guinea-pigs, both number of bacilli and pathogenicity decreased. The glands resembled histologically very much those of Hodgkin's disease. The author believes that the bacilli did not multiply in the animal body.

MAX PINNER.

HUMAN TUBERCULOSIS AT DIFFERENT AGES. ANATOMICAL STUDIES. II. TUBERCULOSIS OF ADULT LIFE. W. BLUMENBERG, Beitr. z. Klin. Tuberk. **62**:711, 1926.

Of fifty-three cases of healed tuberculosis—it was possible to demonstrate the complete thoracic primary complex in forty-nine cases in 40 per cent of these—histologic examination revealed true bone tissue. Only two abdominal primary foci were found. The anatomic studies performed in the technic described in the first communication lead to the following conclusions: The primary pulmonary complexes are not infrequently changed into smooth-walled cavities. The glandular involvement in adults is less pronounced than in the fresh primary complex in childhood. In cases in which no residues of a primary infection

can be revealed, the anatomic results of tuberculous processes are the same as in cases with primary infection. A healed primary infection accordingly does not alter the course of a tuberculosis in adult life, and the adult tuberculosis is conceived not as second or third stage of a childhood infection, but as a disease of its own. With increasing age the indurative changes become more prevalent.

MAX PINNER.

A CASE OF A BACILLUS FRIEDLÄNDER PNEUMONIA SIMULATING PULMONARY TUBERCULOSIS. N. BERGLUND, Beitr. z. Klin. Tuberk. **62**:745, 1926.

A man, aged 52, was sick following an acute onset for almost seven months under the clinical picture of a pulmonary tuberculosis with cavitation. Necropsy showed pleural adhesions, cavities in the right upper lobe, acute bronchopneumonia, a prostatic abscess and acute inflammatory changes in the whole urogenital tract. The causative agent was a Friedländer bacillus.

MAX PINNER.

THE STIMULATING EFFECT OF CERTAIN METALLIC SALTS ON BACTERIAL GROWTH WITH SPECIAL REFERENCE TO THE CULTIVATION OF TUBERCLE BACILLI. K. A. JENSEN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **46**:59, 1926.

In certain concentrations various metallic salts, notably manganese, copper, silver, gold and platinum, stimulate bacterial growth, especially of old cultures. This was found to be true of tubercle bacilli growing on Petroff's medium.

ON THE ACTION OF TOXINS ON THE VESSELS OF AN ISOLATED ORGAN. O. BIRGEN and H. RAWITSCH-BIRGER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **46**: 183, 1926. ON THE INFLUENCE OF TEMPERATURE ON THE ACTION OF TETANUS TOXIN, ibid., p. 189.

The vessels of the rabbit ear react to toxins according to the same laws that govern the reactions to other poisons. At body temperature the vessels of the ear contract violently on the passage of tetanus toxin, but at low temperature there is no contraction.

H-ION CONCENTRATION OF BLOOD IN EXPERIMENTAL TUBERCULOSIS IN GUINEA-PIGS. FRANZ SCHMIDT, Ztschr. f. Immunitätsforsch. exper. Therap. **46**: 386, 1926.

There is no change so long as the process remains local. When the bacilli are scattered over the body there is a slight shift toward the alkaline side (p_H 7.45).

Immunology

A STUDY OF THE PRIMARY TOXICITY OF HETEROPHILE IMMUNE RABBIT SERUM FOR GUINEA-PIGS, AND ITS APPARENT RELATION TO THE PHENOMENON OF ANAPHYLAXIS. WILLIAM W. REDFERN, Am. J. Hyg. **6**:276, 1926.

Tissues of the guinea-pig contain heterophile antigen. Normal guinea-pigs, when receiving intravenous injections with heterophile antiserums, react by a series of typical symptoms often resulting in death. These symptoms take place only when the serum injected contains heterophile antibody. Hence, the reactions appear to be brought about by the combination of specific antibody injected with the antigen in the tissue cells. These manifestations are closely similar to those of anaphylaxis, and in the symptoms preceding death the two reactions cannot be distinguished one from the other.

The conditions within the lungs, however, were found to differ. The lungs of animals killed by primary antiserum injections were markedly hemorrhagic throughout. Much edema also occurred in most cases. This fluid not only filled the lung spaces, but often extended into the trachea and even exuded from the nose. Such a condition was never seen in anaphylaxis. The average weight of the lungs in animals dead from primary toxic shock was also found to be 24.5 per cent greater than the average weight of anaphylactic lungs. This was accounted for by the edematous condition of the former.

Normal guinea-pigs are not protected from lethal doses of heterophile antiserum by previous sublethal injections of either the same antiserum or normal rabbit serum.

The uterine muscle of a normal guinea-pig fails to contract when suspended according to the Schultz-Dale method and treated with heterophile antiserum. The antigen is in the tissue, but contraction of the plain muscle fails to follow introduction of the specific antibody.

Normal guinea-pigs which received injections with horse serum failed also to exhibit anaphylactic responses when treated with rabbit anti-horse-serum twenty-four hours later.

A local reaction, specific in character, follows the intracutaneous injection of heterophile antiserum in the normal guinea-pig. This appears within a few minutes after the injection and persists through a typical series of stages. Necrosis of the local area occurs, and much edema is present. This is followed by sloughing of the tissues.

Efforts to produce immunity against such a reaction or to demonstrate the presence of a specific toxic body formed by the union of antigen and antibody, met with no success.

No toxic body separate from the heterophile hemolytic body could be demonstrated by fractionation of the antiserum by the use of ammonium sulphate.

The cause of death in true anaphylaxis is thought to be primarily due to contraction of the smooth musculature of the body.

From our studies it seems that in primary antiserum toxicity the rapidly increased permeability of endothelial linings and cell membranes is the most significant factor. The hemorrhagic and edematous condition exhibited by the lungs, the hemorrhagic local areas in the skin and the failure of smooth muscle to contract in vitro, all substantiate this belief.

AUTHOR'S SUMMARY.

IMMUNIZATION AGAINST DIPHTHERIA WITH TOXIN DETOXIFIED WITH SODIUM RICINOLEATE. W. P. LARSON and HOWARD EDER, J. A. M. A. **86**:998 (April 3) 1926.

It has been found that substances which lower surface tension, such as sodium ricinoleate, detoxicate bacterial toxins, with the exception of botulinus. The antigenic properties of the toxin remain unchanged. Animals receiving injections with a mixture of diphtheritic toxin and sodium ricinoleate were found to be immune. Several groups of persons with positive Schick tests were given single doses of diphtheria toxin in 1 and 2 per cent soap solution. Of one group, 38.5 per cent were negative after five weeks; of another, 66.6 per cent were negative after eight weeks. There were no reactions to the injections. This method has the advantage over the toxin-antitoxin mixtures in that it does not sensitize to horse serum, there are no reactions, and in the majority of instances a single injection is sufficient.

B. R. LOVETT.

IMMUNIZATION AGAINST SCARLET FEVER WITH TOXIN DETOXIFIED WITH SODIUM RICINOLEATE. W. P. LARSON, E. J. HUENKENS and WOODARD COLBY, J. A. M. A. **86**:1000, 1926.

Sodium ricinoleate is an effective agent in detoxifying scarlet fever streptococcic toxins, and such soap toxin mixtures give a rapid immunity without causing objectionable reactions. The sodium ricinoleate method of detoxication makes it possible to give sufficient toxin in a single injection to cause positive skin tests to become negative within a few days. It opens the possibility of suppressing an epidemic of scarlet fever by active immunization, since 77.3 per cent of positive skin tests become negative in eight days, and 97 per cent become negative in three weeks.

AUTHORS' SUMMARY.

THE EFFECT OF ANTISERUM AGAINST THE SOLUBLE TOXIC SUBSTANCE OF BACILLUS COLI IN BACILLUS COLI PERITONITIS. BERNARD STEINBERG and E. E. ECKER, J. Exper. Med. **43**:443, 1926.

From young cultures of *B. coli* (from eighteen to twenty-four hours) a soluble toxic substance was obtained, and an antiserum against this toxic substance was produced.

The soluble toxic substance is the principal lethal factor when cultures of *B. coli* are injected into the peritoneal cavity of rabbits.

Intravenous administration of the antiserum can avert death in rabbits previously receiving intraperitoneal injections with lethal doses of *B. coli*.

AUTHORS' SUMMARY.

THE REACTION OF COW'S MILK TO BLOOD SERUM PRECIPITIN. F. S. JONES, J. Exper. Med. **43**:451, 1926.

Precipitin tests of cow's milk, with cow's blood serum antiserum from rabbits, reveal during normal lactation a fairly constant proportion of serum that is not influenced by small numbers of bacteria, but is increased by large numbers of organisms, is higher for several days following parturition, and is decidedly increased during acute mastitis. Milk heated to 66 C. for twenty minutes still reacts, but after heating at 68 to 69 C. for twenty minutes produces no precipitate. Suggestions are made that the precipitin may therefore be used practically for the detection of milk from cows with mastitis, and of heated milk.

ETHEL B. PERRY.

UPON THE ANTICOMPLEMENTARY ACTION OF PANCREATIC EXTRACTS. ELLA F. GROVE, J. Immunol. **11**:191, 1926.

The anticomplementary effect of pancreatic extracts, first described by Michaelis and Skwirsky, was ascribed by these investigators to the tryptic ferments. In the present study, it is shown that the ratio of the digestive power of two pancreatic extracts (1:1) may be very different from the ratio of the anticomplementary power of the two extracts (1:100). This observation indicates that the proteoclastic and the anticomplementary functions of a pancreatic extract reside in two different substances. Attempts to separate the two functions in a single extract failed.

S. A. LEVINSON.

REACTIONS OF SENSITIZED GUINEA-PIGS TO INHALED ANTIGENS. H. L. ALEXANDER, W. G. BECKE and J. A. HOLMES, J. Immunol. **11**:175, 1926.

Under certain conditions, the reactions of sensitized guinea-pigs exposed to vaporous antigens are typically anaphylactic in character. Under these conditions desensitization may be accomplished by inhalation of vaporous antigen. To attain these effects it appears necessary to have highly sensitive animals and strong antigens; otherwise, the shocking does not seem to be absorbed in sufficient concentration or speed to be effective.

S. A. LEVINSON.

THE IMMUNOLOGICAL CHARACTERISTICS OF A WATER-INSOLUBLE PROTEIN IN TYPE I ANTIPNEUMOCOCCUS SERA. L. D. FELTON and H. BAILEY, J. Immunol. **11**:197, 1926.

Although definite proofs have not been given of the essential identity of the various antibodies of pneumococci, certain inferences can be drawn from this study. A water-insoluble protein from type 1 antipneumococcus serum, reprecipitated ten times, still has the power of protecting mice against virulent pneumococci, gives positive agglutination, precipitin and complement-fixation tests and stimulates phagocytosis of pneumococci. The protective antibody demonstrated in vivo extends to a greater dilution the other antibodies demonstrated by in vitro immunologic tests.

With the possible exception of one experiment, little evidence has been found to show the possibility of separating the water-insoluble protein into fractions, each with a single immunologic property. Nevertheless, our observations indicate either a separation of the protective from the other antibodies, or an alteration of the protein molecule such that the in vitro manifestations of antibodies are destroyed, without causing decrease in protective power. It is of interest that a relatively pure protein produces all the usual immunologic reactions, and thus the results of these experiments are in accord with the unitarian conception of antibodies.

S. A. LEVINSON.

OBSERVATIONS ON THE HUMAN BLOOD GROUPS. IRREGULAR REACTIONS. ISOAGGLUTININS IN SERA OF GROUP IV. THE FACTOR A^1. K. LANDSTEINER and DAN H. WITT, J. Immunol. **11**:221, 1926.

In human serums there exist commonly agglutinins — "cold" — agglutinins — differing from the well-known iso-agglutinins in that their effect is generally much more diminished by increased temperature. These "cold" — agglutinins, apparently related to and in part identical with auto-agglutinins, display a certain specificity (Bialosuknia and Hirszfeld), and under suitable conditions their effects appear as atypical (minor) iso-agglutinin reactions. The sensitiveness to changes in temperature warrants a differentiation of these substances from the common iso-agglutinins, although agglutinins exist which seem to be intermediate.

Probably there exist other individual differences of human blood than those disclosed by the ordinary iso-agglutination tests.

Strong anomalous iso-agglutinin reactions occur rarely. Neither these nor the minor reactions mentioned previously or the differences disclosed by the use of animal serums have been studied sufficiently to be arranged in a practicable classification.

The division of human blood into four groups is still adequate for ordinary purposes.

The iso-agglutinins acting on corpuscles of group 2 can be separated into two qualitatively different fractions which may be designated as a and a^1.

Among the corpuscles of group 2 (and 4), there are two varieties distinguishable by the different susceptibility to the agglutinin a^1.

Some serums of group 4 contain agglutinins of the type a^1 effective on certain corpuscles of group 2.

S. A. Levinson.

Interagglutination in Spite of Group Identity Between the Blood of the Mother and That of the New-Born. N. de Borchet, Compt. rend. Soc. de Biol. **94**:16, 1926.

In two cases the serum of the mother agglutinated the corpuscles of the infant during the days immediately after birth in spite of the fact that both mother and child belonged to group 2.

The Importance of Using Several Methods Simultaneously for the Serologic Recognition of Syphilis. A. Klopstock and A. Hilpert, Klin. Wchnschr. **5**:265, 1926.

The Serologic Recognition of Syphilis by Several Methods, in Pregnancy and Tuberculosis. Ibid., p. 359.

An agreement in the results of several methods is of greater significance in the serologic recognition of syphilis than is the result of a single method. The surety of the recognition of syphilis when accompanied by pregnancy or tuberculosis is greatly increased when conclusions are drawn from the results of several methods rather than from the result of any one.

Arthur Locke.

Tumors

Studies on the Relation Between Tumor Susceptibility and Heredity. III. Spontaneous Tumors of the Lung in Mice. Clara J. Lynch, J. Exper. Med. **43**:339, 1926.

The relatively high incidence of pulmonary growths among mice of tumor parentage as compared with mice from nontumor parents, and the fact that females from a strain in which pulmonary tumors are rare when crossed with individuals from a strain in which they are frequent give a fairly high rate of incidence of the growths among the first and second filial generations — all these facts indicate that susceptibility to the development of tumors in the lung is an inherited character.

Author's Summary.

On the Frequency of Spontaneous Tumors in the Domestic Fowl. Margaret Schneider, J. Exper. Med. **43**:433, 1926.

Analysis of records from the Storrs Contest, the Harper Adams Trials, and a farm flock indicates an increase of tumors in the second half of the pullet year (May through October) over the first half (November through April).

Some evidence seems to indicate that heavy antecedent egg production is associated with a rise in tumor rate.

The normal annual tumor rate for fowls between the ages of 6 to 18 months is about 2 or 3 per cent.

The appearance of tumors in "epidemic" form probably indicates that the neoplasms found differ in etiology from those on which the normal rate is based.

Author's Summary.

TUMORS OF THE URACHUS: A REPORT OF SEVEN CASES. F. W. RANKIN and B. PARKER, Surg., Gynec. & Obst. **42**:19, 1926.

The urachus may remain patent and not cause any trouble until some disturbance in the bladder or an obstruction to the bladder outlet develops. It may harbor a low grade infection and be the cause of purulent cystitis. The author reports such a case and also one of a cyst and one of an abscess of the urachus. Solid tumors occur, and a case each of a fibroma, an adenoma extending into the bladder, an epithelioma and an inoperable adenocarcinoma are described. One case, clinically tuberculosis of the urachus but not proved so, is also presented.

N. ENZER.

A CONGENITAL CYSTIC TUMOR OF THE NEURENTERIC CANAL. G. H. HAUSMANN, Surg., Gynec. & Obst. **42**:24 (Jan.) 1926.

In an infant, 1 day old, there was found resting on the anterior surface of the sacrum a cystic tumor, which was attached by a pedicle to the anterior surface of the cord through a defect in the sacrum. Histologically, the pedicle had a small lumen lined by epithelial cells, and the wall was made up of glia fibrils and cells. The cyst wall had a stratified squamous epithelial lining, and embedded in the tumor were a few small strands of cartilage, smooth muscle and myxomatous fibrous tissue, nerves and blood vessels.

N. ENZER.

ENDOTHELIAL MYELOMA, EWING. C. L. CONNER, Arch. Surg. **12**:789 (April) 1926.

Fifty-four cases of Ewing's endothelial tumor in bone are analyzed and presented in detail. There are sixty-seven such tumors recorded in the "Registry of Bone Sarcoma" of the American College of Surgeons, constituting 10 per cent of all bone tumors registered. They are found in the long and flat bones, chiefly in children and young adults, and are preceded by trauma and signs of inflammation in 40 per cent. They metastasize to other bones, but with the exception of the lungs, the viscera are rarely involved. Three types are described, angiomatous, reticular and diffuse cellular, but in all the type cell is the same. The cells do not form an intercellular substance that will take the specific stains for collagen, bone or cartilage. The tumor responds quickly to radium. The author considers that the tumor is first solitary; multiple tumors are metastases.

N. ENZER.

ANGIO-ENDOTHELIOMA OF BONE. A. KOLODNY, Arch. Surg. **12**:854 (April) 1926.

Two cases from the "Registry of Bone Sarcoma" are presented as true angio-endotheliomas, and the difference between these and Ewing's endothelioma is stressed. The diagnosis is supported by the fact that tumor cells could be traced to the endothelium of the blood vessels, also by the intimate attachment of groups of tumor cells to the surrounding tissue, their characteristic morphology and the frequent occurrence of intact blood in the alveolar lumens.

N. ENZER.

THE TRANSFORMATION OF MONOCYTES INTO FIBROBLASTS THROUGH THE ACTION OF ROUS VIRUS. ALEXIS CARREL and ALBERT H. EBELING, J. Exper. Med. **43**: 461, 1926.

In normal cultures, the transformation of monocytes into fibroblasts generally occurred when cells became packed together through some mechanical factors that prevented their free migration and determined their accumulation.

Various modifications of the medium, the addition of dead tissue and of trypsin or the products of trypsin digestion failed to bring about the transformation. The inoculation of cultures of monocytes with filtered extract of Rous sarcoma frequently determined the appearance of fibroblasts. The first change undergone by the monocytes cultivated in vitro was a large increase in their size. Later, the giant monocytes became transformed into cells that did not differ essentially from those that grow from a fragment of adult connective tissue.

AUTHOR'S SUMMARY.

PRIMARY CARCINOMA OF THE LIVER. L. S. COUNSELLER and A. H. MCINDOE, Arch. Int. Med. **37**:363, 1926.

Five cases of primary carcinoma of the liver are described: four hepatomas or primary carcinomas of the liver cells and one cholangioma or carcinoma of the bile ducts. The gross and microscopic appearances have little in common, so the massive, nodular and diffuse forms appear in any microscopic type. The massive form is, however, usually derived from liver cells. All the cases were associated with intrahepatic metastasis by way of the portal and the hepatic veins, but in only two were there extrahepatic growths. No transitional forms were found, and the origin is therefore believed to be unicentric. All the cases were associated with cirrhosis of the portal type. The histories in three cases point to a preceding cirrhosis, and in all the microscopic examination of the connective tissue indicated a long standing process. The relation between the hyperplastic liver tissue and the malignant cells is emphasized. From 3 to 4 per cent of cases of cirrhosis, particularly of the portal type, will become carcinomatous.

S. A. LEVINSON.

TESTICULAR ADENOMAS IN AN OVARY. P. MASON, A. CHALIER and J. F. MARTIN, Ann. d'Anat. path. med.-chir. **2**:445, 1925.

On account of metrorrhagia, a left tube and ovary with the broad ligament containing markedly enlarged veins were removed. The ovary was firm, slightly enlarged, glistening gray outside, and contained many small cysts—"sclero-kyetique."

In both the medulla and cortex were epithelial formations regarded as seminiferous tubules chiefly because of a similarity the nuclei possessed to those of sertolian cells. Deeper in the ovary the formations were cords with diameters of 50 to 80 mikrons, sinuous, with no axial lumen, the lining cells filamentous and fused centrally (syncytium). In the cortex the formations were spherical with diameters of 10 to 400 mikrons. Both cords and spherules contained remnants of collagen fibers in various stages of disintegration, ultimately hyaline, rounded masses. The cortical spherules are attributed to proliferation outward of the cords from the root of the ovary where these last originate in syncytial masses of cells in the stroma. All phases of the development of these structures are well illustrated and described. They were interposed with the follicles normal to the ovary, which, however, failed to mature. None of the various stages of spermatogenesis were found in the cells of the "adenomas."

A few years ago one of the authors, Chalier, pointed out the association of varicose tubo-ovarian veins with sclerosed ovaries, and this instance is regarded as supporting that view. The ovarian changes are presumed to precede the development of venous enlargement and tortuosity.

E. R. LECOUNT.

THE REACTION OF NEUTRAL RED IN NORMAL SERUM AND IN SERUM FROM ANIMALS WITH TUMORS. A. H. ROFFO, Bol. d. Inst. de med. exper. **1**:791, 1925.

Neutral red colors serum of normal rats yellow and serum of rats with tumors red. The hydrogen ion concentration and presence of lipoids do not affect the reaction. It appears to depend on physicochemical changes, modifications of the adsorption properties, of the serum from animals with tumors.

B. R. LOVETT.

TUMORS OF THE HYPOPHYSIS IN THE RAT. OLGA FISCHER, Virchows Arch. f. path. Anat. **259**:9, 1926.

In some 200 to 300 necropsies of white rats, Fischer encountered three tumors of the hypophysis. Two of these, which were examined microscopically, were termed carcinomas.

O. T. SCHULTZ.

MORPHOLOGIC DIFFERENTIATION OF CARCINOMA AND SARCOMA. M. COHN, Virchows Arch. f. path. Anat. **259**:30, 1926.

Cohn studied forty-one tumors, paying especial attention to the relation of the supporting tissues to the cells and of the cells to each other, his object being to determine whether such finer histologic details brought out by special staining methods would help in the differential diagnosis of carcinoma and sarcoma. He found that rapidly growing, undifferentiated carcinomas and sarcomas lose those characteristics whose detection by special methods might help in the differential diagnosis.

O. T. SCHULTZ.

METASTATIC CARCINOSARCOMA. H. BALTZER, Virchows Arch. f. path. Anat. **259**:252, 1926.

Robert Meyer and Borst independently have proposed to subdivide neoplasms which are composed of both sarcomatous and carcinomatous elements into composition tumors and collision tumors. In the first group, the stromal and the epithelial elements derived from a single tissue complex are both malignant. In the second group, the admixture of sarcomatous and carcinomatous tissue is due to the mutual invasion by each other of a primary carcinoma and a primary sarcoma, the metastasis of one into the other, or the metastasis of both to the same region, where both elements become intermingled. In the case reported by Baltzer there was a primary giant cell carcinoma of the uterus and a primary cylinder cell carcinoma of the left ovary. The omentum was widely infiltrated by secondary tumor masses, each of which was composed of sarcoma tissue like that of the primary tumor of the uterus and carcinoma tissue like that of the primary tumor of the ovary. According to Baltzer, this is the only recorded example of the metastasis of primary tumors of two organs to a third organ with intermingling of both tumor types.

O. T. SCHULTZ.

VASCULAR TUMORS OF LIVER AND SPLEEN. B. UGRIUMOW, Virchows Arch. f. path. Anat. **259**:366, 1926.

Ugriumow makes a brief report of a case of diffuse capillary ectasia of the liver and one of priamry angiosarcoma of the spleen. The first he considers a developmental anomaly in the sense of Albrecht's hamartoma. The spleen tumor was a hemangio-endothelioma in which the transition from sinus endothelium to tumor alveoli could be traced.

O. T. SCHULTZ.

Medicolegal Pathology

ACUTE MERCURIC CHLORIDE POISONING. L. A. KOHN, Arch. Int. Med. **37**:225, 1926.

Death from mercuric chloride taken by mouth may ensue within hours, apparently with circulatory collapse, with little renal damage and no evidence of uremia. Evidence is presented which suggests that direct myocardial damage may account in part, at least, for this early toxic death. In three severely poisoned cases, the white count reached 34,000 or higher in a few hours, and it is suggested that the degree of elevation of the leukocytes may be an index of the severity of poisoning, with an unfavorable prognosis when levels of from 30,000 to 40,000 are found.

S. A. LEVINSON.

THREE DEATHS FROM INHIBITION. E. and G. FOURNOT, Ann. de méd. legale **5**:89, 1925.

Two of these were deaths following attempts to produce abortion, and in each an instrument was used to force soapy water in the uterus. The fetus was found intact in each, but in one, a few small, worm-shaped clots were in the uterus near the internal os; in the other, the placenta was slightly loosened.

There is no mention of air embolism in the reports, nor is it possible from the accounts to conclude whether air embolism was still demonstrable at the time of the postmortem examinations. That wounds were made and by instruments which may have forced air into the uterus or into torn blood vessels, is obvious. Air embolism should have been looked for as a possible cause for the deaths.

The third death in an obese man, aged 65, was attributed to a trivial jolting in a railroad accident, and although at the time he was apparently in good health, a marked hypertrophy of the heart with evidence of decompensation were found after death.

E. R. LECOUNT.

DEATH BY INHIBITION. M. DUVOIR and C. RICHET, Ann. de méd. legale **5**:193, 1925.

This topic was first on the list of several selected for discussion at the Eleventh Congress for Legal Medicine at Lille last year, and the professors of the faculty of medicine in Paris, Duvoir in legal medicine and Richet in physiology, made the chief report.

From a questionnaire sent to fifty persons with extensive experience in animal experimentation, asking whether they had observed death in animals from inhibition, thirty answers were received, sixteen "No," ten "Yes," four "doubtful."

Most of the evidence of death from inhibition has come from work with animals, and to a considerable degree the conditions and results are not applicable to human experience. The usual cardiac, pulmonary and cerebral forms of inhibition are reviewed, and to these the writers add a fourth, a systemic cellular inhibition typified by anaphylactic shock. They review a great variety of ways in which death due to inhibition may occur, but, so far as their usefulness in dealing with explanations for deaths of human beings is concerned, their account is unconvincing.

The deaths, for example, which follow the first whiff or two of chloroform in persons with lymphoid tissue hyperplasia and persistent thymus, are perhaps as good as any illustrating so-called cardiac inhibition, but the possibility that they are instances of pure acute chloroform poisoning in persons rendered

unusually susceptible by disease is not considered. In place of burial with cardiac inhibition as the inscription, there should be study of the conditions which increase susceptibility to chloroform. And similar considerations apply to all the other forms of death by inhibition, because the reports of deaths so brought about are amazingly defective in thorough microscopic studies, chemical examinations and in opportunity to obtain adequate postmortem examinations soon after death.

E. R. LeCount.

Critical Summary of the Present Status of Individual Blood Diagnosis for Forensic Purposes. Reinheimer, Deutsche Ztschr. f. d. ges. gerichtl. Med. **6**:560, 1925.

The author concludes that iso-agglutination rests on a firm basis. At present it does not seem likely that it concerns more than two iso-agglutinins and two iso-agglutinogens. Once developed, the iso-agglutinins remain permanent and unchanged in their grouping from environment or disease. The inheritance of blood grouping according to mendelian principles seems to be established. In view of the facts stated, it would seem that determination of blood grouping may yield results of value for forensic purposes. Where blood grouping alone is not sufficient to determine the precise person to whom a particular blood belongs, under certain conditions the determination that a given specimen of blood does or does not belong to the same group as a given person or persons obviously may be of great significance. The usefulness of blood grouping for forensic purposes will be limited by the fact that blood spots and the blood in cadavers do not retain their group specific properties very long. The time seems ripe for studying results of iso-agglutination for forensic purposes under controlled conditions so that their practical value may be determined.

Technical

Methods of Staining Tubercle Bacilli. H. J. Corper, J. Lab. & Clin. Med. **11**:503, 1926.

An examination of 20 sputum smears containing tubercle bacilli by thirteen different staining methods (Koch, Ehrlich, Ziehl-Neelsen, Andrejew, Spengler, Much, Gasis, Herman, Fontes, Konrich, Burke and Dunning, Serkowski and Biot) revealed that when the technic is properly performed the majority of these methods may result in staining the tubercle bacilli in the sputums with equal efficiency. There was, however, a decided difference in the ease of performance, speed and simplicity of the various individual methods. Sixteen different positive sputum smears consecutively stained and restained (after destaining) by nine different methods (Ziehl-Neelsen, Andrejew, Herman, Konrich, Gasis, Fontes, Burke and Dunning, Ehrlich, and Spengler) emphasized further the importance of technic in the staining of tubercle bacilli. Much's (Gram) method alone proved unsatisfactory with sputum on account of the difficulty of differentiating tubercle bacilli from other small cocci and dye precipitates, since in the majority of cases only the granules stain. Double bacillary staining (carbolfuchsin-Gram, Much) of sputum and pus did not increase the efficiency of the simple single bacillary carbolfuchsin stain but increased the cumbersomeness of the technic. For practical purposes the simpler methods have the advantages of speed and simplicity. The finding of acid-fast bacilli (with the usual clinical precautions) practically certifies a diagnosis of tuberculosis by the methods, while the presence of Gram (Much) granules alone requires corroborative positive animal inoculation results to certify the diag-

nosis. It is for this reason that the Gram (Much) granules and combined methods are mainly of academic interest. It does not seem that the Gram granules differ from the granules seen in appropriately stained carbolfuchsin preparations since their numbers, morphology and location appear to be identical. Preparations stained first by the Gram (Much) method followed by the modified Ziehl-Neelsen carbolfuchsin-acid alcohol technic reveal only blue granules in a red bacillus. Red and blue granules in a lighter red bacillus were never noted. For practical purposes the simple steaming carbolfuchsin (Ziehl-Neelsen) method for staining tubercle bacilli, or one of its modifications, is recommended to the clinical pathologist. The choice of colors remains with the individual operator since any number of dye combinations can be used for staining and counterstaining tubercle bacilli. A negative finding by the simple method requires for further elaboration animal (guinea-pig) inoculation, because as many as a million bacilli (about 0.000.1 mg.) per cubic centimeter material is hardly discernible microscopically while from 10 to 100 bacilli from a culture freshly isolated from sputum suffice to infect a guinea-pig. In view of the danger of technical errors and in order to raise the present efficiency of the technic, especially with otherwise negative results or when only single specimens are available, it is recommended that each specimen tested for tubercle bacilli by staining methods be controlled by the coincident staining of a like preparation to which a standard suspension of tubercle bacilli, which can easily be kept available in the laboratory at all times, has been added.

AUTHOR'S SUMMARY.

THE SEDIMENTATION RATE OF ERYTHROCYTES IN THE DIAGNOSIS OF ACTIVE TUBERCULOSIS. M. POPPER, Rev. Tuberc. **6**:497, 1925.

This test must always be considered in conjunction with all other clinical and laboratory results; then it is of great value. An increased rate is a strong argument for the diagnosis of an active tuberculous lesion.

GALLOZYANIN (BECHER) AS A NUCLEAR STAIN, WITH A FEW REMARKS ABOUT THE STAINING AND SILVER IMPREGNATION OF GELATIN SECTIONS. CARL KRAUSPE, Centralbl. f. allg. Pathol. u. path. Anat. **36**:392, 1925.

A method is given for using gallozyanin as a nuclear stain in sections embedded in gelatin. It cannot be used for celloiden sections. After the frozen sections are cut, they are stained in gallozyanin solution for from 12 to 24 hours at 37 C. The section is washed, placed on a slide previously spread with from 10 to 20 per cent of gelatin solution, and blotted with paper dipped in 10 per cent formalin. This attaches the section to the slide. The latter is dipped in 50 per cent alcohol for five minutes, and then counterstained with almost any other stain desired. If sudan III is used, the slides are left in for about an hour.

In using silver stains, it is sometimes useful to place the sections in weak ammonia solution for several hours and then in distilled water for twelve hours before staining in the usual way.

B. R. LOVETT.

A MICROMEINICKE REACTION IN HANGING DROPS IN THE DARK FIELD. W. HARTWICH, Klin. Wchnschr. **4**:2518, 1925.

A technic is developed for the rapid examination of syphilitic serums by the Meinicke flocculation reaction. A hanging drop of the flocculation mixture is observed microscopically in a dark field. Details are given.

ARTHUR LOCKE.

Society Transactions

AMERICAN ASSOCIATION OF IMMUNOLOGISTS

Thirteenth Annual Meeting, Albany, N. Y., April 1 and 2, 1926

W. H. MANWARING, M.D., *President*
A. F. COCA, M.D., *Secretary*

PRESIDENT'S ADDRESS. W. H. MANWARING.

After discussing some of the results that have lead to the belief that physiologists and pharmacologists are fully justified in their skepticism of all phases of immunology directly or indirectly based on the Ehrlich specific receptor hypothesis, Dr. Manwaring concluded as follows: "It is even conceivable that the future will show that the wide acceptance of the Ehrlich theory by practical serologists and clinicians, and particularly the prominence given to this theory in elementary textbooks in bacteriology, constitute today our most serious handicap to immunologic progress, both in theoretical and in practical lines.

"I think we would win the endorsement of physiologists and pharmacologists if we would lay aside for future reference the entire scheme of immunology based on the specific receptor hypothesis, and would begin anew, at the very beginning, to unravel the mystery of the origin and nature of antibodies, directing our attention, first, to problems relative to the normal and pathologic permeability of fixed tissues and wandering cells for immunologic antigens, and second, to problems relative to the interplay of antigens with extracellular and intracellular, hydrolyzing and synthesizing enzymes.

"It would be comparatively easy to work out a consistent theory of immunity, based on the assumption that antibodies are slowly synthesized in the body by the action of these enzymes and by them are specifically adapted to injected antigens or to primary and secondary products of antigen hydrolysis. Such an assumption, of course, may be just as visionary as the discarded receptor hypothesis, but it would have the advantage of being more nearly in accord with the known facts of cellular biology. Above all, it would stimulate the hope that in time therapeutic antibodies, possibly even superior to those formed in the animal body, may be successfully synthetized in the chemical laboratory.

"The possibilities of serum therapy are by no means the closed book our critics would imply."

THE NATURE OF THE HEMOLYSINS OF NORMAL AND IMMUNE SERUMS. ARTHUR LOCKE, E. R. MAIN and E. F. HIRSCH.

The nature of the hemolysin-erythrocyte equilibrium indicates that there is in amboceptor serum a substance, probably derived from the injected antigen, which is capable of binding hemolysin and restraining its adsorption on added cells. The degree of the characteristic properties of an immune serum, such as specificity, avidity and thermostability, is shown to be dependent on the amount and character of this binding substance dispersed in the serum. The substance is adsorbed by erythrocytes together with hemolysin, and when the

hemolysin is recovered from the adsorption its protein content is proportional to a constant plus the calculated protein content contributed by the binding substance. The properties of the hemolysin may be changed by changing the proportion and character of its binding substance content. It is postulated that antibodies are composed of clusters — of relatively large dimension — in which an elementary, naturally occurring, protein substance is adsorbed in preponderating amount on nuclei of a binding substance derived from the injected antigen, and that they owe their individual properties to the proportion and character of this binding substance. A mechanism is suggested for the production of immune antibodies in the living organism.

STUDIES OF THE MECHANISM OF SPECIFIC BACTERIAL AGGLUTINATION. GERALD S. SHIBLEY.

The specific effect of twelve immune agglutinating serums on the cataphoretic charges of their homologous organisms has been determined. The bacteria investigated were pneumococcus type 1, *Streptococcus scarlatinae, Staphylococcus aureus,* meningococcus, a diplococcus variant of a streptococcus, *B. coli, B. typhosus, B. paratyphosus* A, *B. tuberculosis,* and three strains of dysentery bacilli: Shiga, Flexner and Mt. Desert. When the charge on the bacteria is high without serum, this charge is specifically reduced; when low, it is raised. In all cases, no matter what the initial charge (the range was from 5 to 40 millivolts), high concentrations of serum, over 1:50, bring the charge to a common potential level, about from 8 to 14 millivolts. Loeb has shown that protein coated collodion particles assume the cataphoretic charges of the proteins. The common potential level of the bacteria treated with agglutinating serums is probably explained therefore on the basis of a coating of the organisms by a common protein, that is, the globulin-agglutinin complex. Additional evidence that this assumption is correct was obtained when sensitized pneumococci compared with euglobulin particles obtained from pneumococcus antiserum showed identical cataphoretic charges under similar experimental conditions, and when sensitized colon bacilli compared with denatured pseudoglobulin gave similar results.

Loeb has shown that collodion particles coated with crystalline egg albumin behave with regard to cataphoretic charge and stability in suspension as if they were particles of denatured albumin. We have confirmed these findings in the case of pseudoglobulin (one of the globulins entering into the globulin-agglutinin complex).

Bacteria treated with specific agglutinating serum act with regard to cataphoretic charge and stability in suspension as if they were particles of denatured protein. It is probable therefore that we are justified in concluding that the specific bacterial agglutination consists of two steps: (1) the bacteria are coated selectively by the specific agglutinin (globulin), and (2) the globulin coated particles act thereafter as particles of denatured protein and flocculate.

THE POSSIBLE WEIGHTS OF ANTIBODY SUBSTANCE IN IMMUNE SERUMS. F. M. HUNTOON.

If we assume that antibody is an organic chemical substance which produces its typical action by a direct combination with the antigen involved, it becomes possible to evaluate in some degree the amount of this substance which is present in immune serums, and to obtain some idea of the purity of the so-called antibody solutions which have been produced.

Antibody is either protein or nonprotein in its nature. If protein in nature and of globulin-like construction, the size of the antibody molecule is probably not more than 4 millimicrons on a side, or with a volume of 64 cubic millimicrons. Since the specific gravity of the protein solutions is close to that of water, it is sufficient for the purpose of the argument to assume that the weight of this molecule would be the same as that of the same volume of water.

The smallest conceivable amount of antibody that could cause agglutination would be the combination of 1 molecule with 1 organism.

In the case of the typhoid bacillus in which a standard of one billion organisms per cubic centimeter is employed as a test dose, the amount of antibody involved would be 64 billion cubic millimicrons, or 64 cubic microns. Since the usual typhoid serum contains 10,000 agglutinating units per cubic centimeter, the amount of antibody substances in 1 cc. is 10,000 times 64, or 640,000 cubic microns, and in 100 cc. would be 64,000,000 cubic microns, or in terms of weight, 0.064 milligrams.

If we assume that antibody is not a protein and as the smallest possible size consistent with a colloidal substance is 1 millimicron in size, the amount in this case would be 0.001 of a milligram per 100 cubic centimeters of a typhoid serum with a titer of 1 to 10,000. These are the lower limits of the possible amount of antibody substance which can be present.

Now if we compare some of the direct measurements which were obtained by Ottenberg and Stenbuck in their highly purified solution of typhoid agglutinins, we find that their solution if calculated on the basis of 10,000 units per cubic centimeter contained 0.29 of a milligram per cubic centimeter of protein, or 29 milligrams per hundred cubic centimeters.

If a single agglutinating dose of this solution is divided among the billion organisms of the test, it is found that there is approximately 29,000 cubic millimicrons available for attachment to each organism, which calculated on the basis of the size of the globulin molecule would allow for the attachment of 450 molecules.

Dr. Ottenberg has kindly furnished me with unpublished figures concerning the total organic solids of this highly purified solution. It is found that the nonprotein organic solid when calculated on the basis of 10,000 units per cubic centimeter amounted to 60 milligrams per hundred cubic centimeters, so that regardless of the protein, or nonprotein nature of this substance, we are justified in assuming that the outside limit of the amount of antibody in a typhoid agglutinating serum of 10,000 titer is in the case of protein 29 milligrams per hundred cubic centimeters, and if nonprotein, 60 milligrams, so that we can assume that the limits of antibody substance in this serum lie between 0.001 of a milligram and 60 milligrams per hundred cubic centimeters.

It is interesting to note in this connection that in Dr. Ottenberg's experiment in their original solution the relation of protein to the non-nitrogenous substance was approximately 2 to 1, whereas with the final purified product the relation of protein to non-nitrogenous substance was 1 to 2.

Locke and Hirsch, working with hemolytic serums, have obtained solutions in which 0.000125 mg. of protein are associated with each hemolytic unit, which in a serum with a titer of 1:10,000 would give 1.25 mg. per cubic centimeter, or 125 mg. per hundred.

Felton working with the antibodies of antipneumococcus type 1 serum has published some interesting figures bearing on this point. He has taken as a standard for protection against type 1 pneumococcus the amount of serum or purified product which will just protect mice against one million fatal doses. He publishes no figures as to the total organic solids, but made extensive

observations on the nitrogen content of both raw serums and the purified product with which he was working. The lowest figure which I have been able to find in Felton's tables indicates a nitrogen content of 0.01 of a milligram per protective dose, or in terms of protein, 0.0625.

Since an average of 13 protective serums tested by Felton gave a dilution of 1:30 as containing a protective dose, in 1 cc., 0.0625 times 30 times 100 gives the amount of protein associated with the protective substance, or 187.152 mg. per hundred cubic centimeters in the average pneumococcic protective serum.

In my own work with pneumococcus antibody solution prepared in a different manner than Dr. Felton's, I have found that on testing them against his protective standard they give a nitrogen and protein content somewhat lower per protective dose. An average of 5 determinations on different lots of antibody solution gave a trifle over 0.003 mg. nitrogen per protective dose, or 57 mg. of protein for 100 cubic centimeters of average serum. The nonnitrogenous factor in the same determination averaged 0.013 mg. per dose, or 39 mg. per hundred cubic centimeters for serum.

Possible Weights of Immune Substance in Serums—F. M. Huntoon

	Organic Content Antibody Solutions		Calculated Content for Serum		
	Weight per Unit			Weight in 100 Cc.	
Antibody Solutions	Mg. Protein	Mg. Non-Nitrogenous	Titer	Mg. Protein	Mg. Non-Nitrogenous
Ottenberg and Stenbuck: Typhoid.....	0.000029	0.00006	10000	29	60
Locke and Hirsch: Hemolytic.....	0.000125	.....	10000	125	..
Felton: Type 1 protective pneumococcus	0.0025	.....	Average value	187	..
Huntoon: Polyvalent protective pneumococcus	0.019	0.013	Average value	57	39
	Total Organic			Total Organic	
Monovalent type 1.....	0.014 mg.			42 mg.	
Same, purified, concentrated 20 X.....	0.0054 mg.			16.2 mg.	
After adsorption by type 2.....	0.00625 mg.			15.75 mg.	
Readsorbed with type 1					
Relation of lost weight to lost protective units	0.00034 mg.			1.02 mg.	

In the final type 1, adsorption of loss of weight of 33 mg. per hundred cubic centimeters was accompanied by a loss of 96,000 protective units per hundred cubic centimeters.

An attempt was made to approach the problem in a different manner. In this experiment only total organic weight was taken into consideration. A monovalent type 1 antibody solution was concentrated 20 times per volume with apparently no loss of antibody content and a decrease in the total organic solids from 0.014 mg. organic material per protective dose to 0.0054 mg. This concentrated solution was then adsorbed with type 2 organisms which had been washed repeatedly, first with salt and then with distilled water, and finally dried in vacuo; this adsorption resulted in no loss of type 1 protective substance, but in a reduction of 10 mg. per hundred cubic centimeters in the weight of the solutions. The solution adsorbed by type 2 was then readsorbed with a type 1 organism treated in the same manner. It was found that a direct loss of weight of 33 mg. per hundred cubic centimeters resulted with a coincident reduction of antibody content from 128,000 to 32,000 protective units per hundred cubic centimeters. This gives a relationship of 0.00034 mg. to each protective dose, or, expressed in terms of antibody content of the average serum, gives 1.03 mg. per hundred cubic centimeters. The question arises here whether the organisms themselves have not dissolved to some extent in the solution which

would apparently decrease the adsorbed weight. On the other hand, a non-specific adsorption from the solution such as occurred in the type 2 adsorption would increase the adsorbed weight. Since the preliminary treatment of the organisms employed tended to remove not only the salt content, but most of the dissolvable material present, and the fact that the adsorbed solution after centrifugation was not only clear, but brilliant in appearance (no opalescence due to dissolved organisms), leads to the conclusion that this method produces results of approximate accuracy, especially when the result obtained, 1 mg. per hundred cubic centimeters, is compared with the lowest figure obtained by direct measurement of organic content, namely 15 mg. per hundred cubic centimeters.

A consideration of the figure arrived at (1.03 mg. per hundred) in connection with the number of organisms involved in either the protection test or the agglutination test with pneumococcus serum, leads to the conclusion that this figure is still too large, but it does offer a tentative standard for the measurement of the purity of antibody solutions that are produced by various methods.

DISCUSSION

ON PAPERS OF ARTHUR LOCKE, E. R. MAIN AND E. F. HIRSCH; G. S. SHIBLEY, AND F. M. HUNTOON

STUART MUDD: I should like to ask Dr. Locke whether it is possible to explain by your theory the large amount of antibody that may result from introduction of a relatively small amount of antigen?

It has been possible to show by a method entirely independent from that used by Dr. Shibley that homologous serum coats the acid-fast bacteria, also, with a film of antibody. The unsensitized bacteria have the miscibilities of lipin particles; the sensitized bacteria behave like hemoglobin crystals or casein films on milk droplets.

L. DIENES: I should like to ask Dr. Huntoon whether the agglutination with very potent serums was used for the determination of the possible amount of antibodies in the immune serum? In the dilution 1:1 million of the serum, the amount of protein substances present, calculated to a single bacterium, is not very far from the weight of a protein molecule.

ARTHUR LOCKE: If the immune antibodies are produced by the disintegration of aggregates of natural antibodies adsorbed on the injected antigen, as postulated, the extent of the antibody response, as measured by the titer produced, could hardly be directly proportional to the amount injected except within restricted ranges. It would be limited (*a*) by the quantity of natural antibody available for adsorption, and (*b*) by the rate at which it becomes available as contrasted to the rate at which the binding capacity of the antigen becomes modified by disintegration. We find, therefore, that (*a*) when larger amounts of antigen are injected, the titer of the antiserum produced is higher than when smaller amounts are injected, but not proportionately higher; and that (*b*) when rapid adsorption of natural antibodies is facilitated, as by intravenous injection of the antigen, the antibody response to a specified amount of antigen is proportionately greater than when the antigen is injected intraperitoneally when the adsorption-disintegration rate ratio is considerably less. The antibodies produced from the larger injections usually contain a proportionately larger quantity of binding substance and have a lower avidity.

A Hitherto Undescribed Anomaly in Blood Groups. Reuben Ottenberg.

In a case of splenomegaly in a woman, aged 46, with cirrhosis and ascites, hemolysis with a subsequent acute failure of liver function followed transfusion. The donor's blood contained an abnormal agglutinin active not only against the cells of the patient (who like him belonged to group 3), but also against cells of groups 1, 2 and 3. It behaved practically like the blood of a foreign species. It can be inferred that: 1. Donors whose serum agglutinates the cells of the patient (for example "universal" donors, group 1, for patients of groups 2, 3 and 4) are not necessarily safe. 2. Hemolysis if it occurs is particularly dangerous in diseases of the liver and spleen. 3. It is not enough in transfusion to depend on identity of groups. "Cross tests" of donor's and patient's serum on each other's cells must invariably be performed. By this means the danger of hemolysis due to subgroups or rare anomalies can be completely avoided.

DISCUSSION

M. W. Lyon: In the case of two persons belonging to group 4, the serum of each agglutinated the corpuscles of the other.

R. Mellon: Was a fragility test made?

P. J. Manheims: Has cross agglutination been observed in group 3?

R. Ottenberg: The fragility test had given normal results. It was probable that disturbances had followed the use of the donor in other cases. The agglutination could not have depended on the C elements of Guthrie and Huck.

Sero-Anthropological Investigations Among Some Races in Roumania. Sabin Manuila.

The remarkable investigations made by L. and H. Hirschfeld (*Lancet*, Oct. 2, 1919, p. 675), who have examined 7,900 persons belonging to fourteen different races, showed that the distribution of blood groups is correlated with the race, although the anthropologic significance of the blood group distribution is not yet known. In order to aid in the solution of the anthropologic problem of blood grouping, we have started to examine the different races

Distribution of Blood Groups in an Examination of 4,469 Persons

Race	Number of Examinations	O 1	A 2	B 3	AB 4	Index
Roumanians	1,521	7.4	43.3	15.6	33.7	2.2
Saxons	301	4.0	50.5	12.0	33.5	3.4
Germans	414	3.9	42.1	14.0	40.0	2.6
Slovaks	461	8.2	31.3	15.8	44.7	1.7
Ruthenians	400	20.3	39.2	22.5	18.0	1.4
Hungarians	688	11.2	40.8	20.2	27.8	1.6
Bulgarians	372	8.3	45.4	14.8	31.5	2.3
Jews	211	15.3	38.8	19.8	26.1	1.6
Others	101	....	....	....	....	...
Total	4,469					

from Roumania. The total number of examinations made in this Institute is nearly 20,000, from which 4,469 were made by myself, 2,512 by Popoviciu and myself (*Compt. rend. Soc. de biol.* **90**:542, 1924), and the rest by Vonica and myself (unpublished), and by Popoviciu (*Compt. rend. Soc. de biol.* **90**:1069, 1924).

Our investigations of these 4,469 persons in Roumania resulted in findings which coincide with those of other investigators of these same races in different countries, indicating the anthropologic value of blood group determination.

The index for the Roumanians as given in the table agrees with that of the Bulgarians, Serbs and Greeks examined by L. and H. Hirschfeld, which suggests a close relationship between the peoples of the southeastern European nations. This result is in agreement with the modern theories of historians and anthropologists.

The Slavs from the north (Russians, Ruthenians, Czechoslovakians and Poles) have a close sero-anthropologic relationship. At the same time, their blood structure is entirely different from the blood of the southeastern European nations. We may say that the northern Slavs are closely interrelated, and the same statement holds for the southeast European people, but these groups seem to be sero-anthropologically independent of each other.

In the eight races included in this investigation, the sero-anthropologic classification agrees with that of the anthropologist. The method of isohemagglutination seems to be a valuable tool in the study of racial determination.

THE PROBABLE ERROR OF A RACIAL BLOOD INDEX. L. J. REED and SABIN MANUILA.

Following the work of L. and H. Hirschfeld, it has become customary to use as an anthropologic index the ratio of the total number of persons in blood group A to the total number in group B. The use of such an index as a characteristic of a race is obviously a sampling proposition, for at best we can test but a small proportion of any one race, and we must then use the ratio for this small sample as an index of the race as a whole. It is obvious, therefore, that we need to take some account of the variation that may occur in such an index through simple sampling. To measure this variation we have developed the following equation for its probable error. If the index is given by the equation:

$$I = \frac{A + AB}{B + AB}$$

then the probable error of I is expressed by:

$$\text{Probable error of } I = 0.67449\ I \sqrt{\frac{A + B}{(A + AB)\ (B + AB)}}$$

The probable error of any index as computed by this formula may be used in the usual way. If, for instance, we wish to compare the indexes of two races, we compute the probable errors of these two indexes, take the difference between the indexes, and then compute the probable error of this difference by the following formula:

$$\text{Probable error of } (I_1 - I_2) = \sqrt{(\text{P. E. of } I_1)^2 + (\text{P. E. of } I_2)^2}$$

To determine whether or not such a difference is significant, that is, whether or not it is likely to have arisen through the variation of the sampling process, we divide the difference between the two indexes by the probable error of the diffeence, and then with this quotient look up the degree of significance as given in table 40, page 218, "Medical Biometry and Statistics" by Raymond Pearl. Such a procedure is essential in the use of the racial blood index, if we are to avoid drawing conclusions on the strength of differences that may be insignificant.

THE INCIDENCE OF THE LANDSTEINER BLOOD GROUPS IN THE AINU AND SOME FILIPINO TRIBES. ELLA F. GROVE.

The occurrence of the blood groups was studied according to the plan of the Hirschfelds and of Ottenberg among 304 Ainu, 55 in the village of Shin and 249 in Piratori. The race graph of these Ainu is very different from that of

Ainu examined in Kamikawa and in the island of Sakhalin (together 405 persons), but is quite similar to that of the Koreans examined in Chukaku and Zenan (together 283 persons).

The blood group feature of 442 Sulu Moros and that of 501 Samal Moros were found to be quite different, that of the former resembling closely that of the typical Malay, and that of the latter resembling that of the Hindus. The race index of the Samal Moros (0.52) is the lowest yet observed.

These results reveal a serious limitation to the use of the Hirschfeld method of characterizing peoples, in that a great difference is found between the blood group features of two groups of identical people, and a close similarity is found in the blood group features of two distinctly different peoples.

It would seem proper to look on the race index or the race graph as representing a single feature, with which *alone* one should no more expect to determine racial relationships than with any other single feature.

NOTE.—Since this was written, the important paper of Lowell J. Reed and Sabin Manuila on "The Probable Error of the Racial Blood Index" was read, and it was thought possible that that contribution would necessitate a modification of the foregoing conclusions. I therefore submitted the results to Dr. Reed, who kindly reviewed them and expressed himself as in agreement with the conclusions, but from a quite different point of view. He demonstrated the possibility on the basis of chance in the selection of subjects, of harmonizing the different results obtained in the same people. But he also showed, on the same basis, the possibility of harmonizing the different results obtained in different peoples that hitherto have been considered significant.

Hence the statistical principle introduced by Reed and Manuila into this field of investigation, while it will necessitate a complete revision of the reported results, does not affect the validity of the conclusion expressed above.

THE BIOLOGIC ORIGIN OF INAGGLUTINABILITY OF FRESHLY ISOLATED TYPHOID CULTURES. RALPH R. MELLON.

It has been shown that in the colon-typhoid group it is possible to dissociate variants which are serologically related to the parent form. The derived or variant form contains specific agglutinogen (*minor* agglutinogen) while the parent form represents the group agglutinogen (*major* agglutinogen). This well-known relationship really states that the "*group*" antiserum contains agglutinin for both group and specific organisms, while the "specific" antiserum contains agglutinin for the specific or homologous organisms only.

Under these conditions the group antigen does not agglutinate in the serum of the specific organism and gives negative or equivocal results on absorption. By cataphoretic methods it has been possible to show that these so-called specific serums actually contain some group agglutinin, and the lack of agglutination is to be referred to surface alterations of the cell that prevent agglutination. The mechanism of the phenomenon appears to be as follows:

It can be shown, for example, that the "group" antigen is actually sensitized in the "specific" serum, as indicated by the drop in the electric charge of the organisms; but at the same time the organisms adsorb to an even greater extent the nonspecific inhibitory substances out of the serum. These prevent complete or firm binding of specific agglutinins, as can be shown by the apparent ease with which the latter are removed by washing in distilled water. The electric charge is an indicator of this removal, because it returns to its original level and often to higher levels than before sensitization.

What is interpreted tentatively as a preferential adsorption of nonspecific inhibitory substances, can be partially compensated by carrying out the whole agglutination technic at 20 C., which results in partial or complete agglutination. However, some of the variants are refractory even under these conditions. Further evidence that the effect is primarily a surface change in the bacterial cell is shown by the fact that an inagglutinable freshly isolated *B. typhosus* when grown on 0.1 cystine agar was completely and specifically agglutinable. It has also been shown that such strains will adsorb out certain of these inhibitory substances from immune serums. The inagglutinable strains differ among themselves, as shown by individual adsorption preferences for these inhibitory substances, of which there appears to be a plurality.

The results have a special interest because these variations in agglutinability, both specific and nonspecific, are conditioned by genetic alterations in the bacterial cells. The latter are definitely an expression of the life cycle of the organism involving particularly its sexual phase (zygospore formation). A certain practical and taxonomic significance attaches to the fact that morphologically the variant strains were so diverse as to cause no suspicion of serologic relationship.

REPORT ON A SPECIFIC FLOCCULATION REACTION BETWEEN ALCOHOLIC EXTRACTS OF PNEUMOCOCCI AND ANTIPNEUMOCOCCUS SERUM. C. W. JUNGEBLUT.

A flocculation reaction has been described which occurs between alcoholic extracts of pneumococci, reinforced by benzoin tincture, and antipneumococcus serum. The reaction appears to be species specific and type specific; it is apparently dependent on the use of comparatively fresh serums, since a number of antipneumococcus serums older than one year flocculated slightly or not at all. The flocculating power of the serum from five horses undergoing immunization with pneumococcus type did not develop to any extent before the end of the fourth month. In the case of two of these horses in which it has been possible to carry out parallel tests on a larger number of subsequent bleedings a distinct relationship was noted between the flocculating power and the protection titer. The results obtained so far suggest the value of further study of this reaction in the type diagnosis of pneumonia and the standardization of type 1 antipneumococcus serum.

STUDIES ON THE PROTECTIVE SUBSTANCE IN ANTIPNEUMOCOCCUS SERUM. STUDY V. SOME OF THE PROPERTIES OF THE PROTEIN CONTAINING THE PROTECTIVE ANTIBODY. LLOYD D. FELTON.

The paper contained a study of a water-insoluble protein having protective characteristics of antipneumococcus horse serum as compared to the water-insoluble protein (euglobulin) in normal horse serum. Material for study was obtained by diluting 10 to 20 liters of immune serum of each type with 10 volumes of distilled water acidulated sufficiently to give the diluted serum a p_H of 6.8. Normal serum was brought to p_H 6, instead of 6.8 to obtain a maximum yield. The precipitates were washed once with distilled water and then dissolved in 2 per cent sodium chloride. This solution was filtered and again diluted with 10 volumes of distilled water. The process of dissolving in sodium chloride and precipitating by subsequent dilution was carried out seven times, and the final precipitates washed once with 10 liters of distilled water.

It was found by performing the typical acid-base titration procedure of a protein that the hydrogen ion concentration of minimum solubility of the protein derived from antipneumococcus serums lay between p_H 5.9 and 6.4, while that of the euglobulin gave the classical result of p_H 5.4. Other characteristics were found as follows: Protein from immune serums was almost completely precipitated by 38 to 42 per cent saturation with ammonium sulphate or with 15 to 18 per cent sodium sulphate, whereas the euglobulin was precipitated at saturation of 30 to 32 per cent ammonium sulphate and 11 to 12 per cent sodium sulphate. Per unit of protein, euglobulin contained the highest concentration of phosphorus. In estimation of the protective strength and agglutinating titer of the solution at different hydrogen ion concentrations (members of the acid-base titration series), it was found that in the acid solution, p_H 5 to 6.4, the amount of protein in solution was a rather close index of the titer of the two biologic tests; whereas in the alkaline solutions, the titers of the biologic tests were greatly reduced.

THE BACTERIAL ACTION OF THE SERUM FOLLOWING INJECTION OF EPINEPHRINE. GEORGE H. SMITH.

Injections of epinephrine 1:1,000 increased the bactericidal action of the serum of rabbits on typhoid bacilli. Large amounts of epinephrine reduced the effect.

DISCUSSION

R. OTTENBERG: Was the bactericidal substance in the serum heat resistant?

G. H. SMITH: Partly.

HETEROPHILE ANTIGEN-ANTIBODY REACTIONS IN RELATION TO THE SERUM DIAGNOSIS OF SYPHILIS. SANFORD B. HOOKER.

An immune heterophile serum (anti-hen erythrocyte) when tested with various Wassermann and Kahn "antigens" flocculated powerfully in mixtures with alcoholic extracts of heterogenic tissues (horse and guinea-pig) but not with similarly prepared extracts from nonheterogenic sources (human, bovine and porcine). Since the natural antisheep hemolysin present in varying amounts in most human serums is considered to be of heterophile character, and since its existence is not connected with syphilitic infection, it was thought that falsely positive reactions due to the operation of a heterophile antigen-antibody mechanism might sometimes occur when heterogenic extracts were employed in the precipitation and possibly the alexin-fixation technics used in the serum diagnosis of syphilis.

Tests of this hypothesis on several hundred serums with Kahn's precipitation method and antisheep hemolysin titration, disclosed a definite numerical association of high lysin content with *falsely* positive precipitation of horse and guinea-pig lipoid emulsions. Discrepant reactions, however, in both directions, were not infrequent. Tests with specific and control absorbing agents occasionally also have yielded results which are so far inexplicably at variance with the assumption that lysis of sheep cells and precipitation of heterogenic extracts are mediated by the same reacting substance in every serum. Whatever be the mechanism, the frequent occurrence of syphilitically nonspecific precipitation warrants this cautionary discussion, particularly since the Vernes method, as well as Meinicke's third modification, prescribes the use of horse heart extract.

About a thousand parallel Wassermann tests, using beef and horse heart antigens prepared by Kolmer's method, have failed definitely to show any correlation of high lytic potency and certain stronger reactions with the horse heart extract. A wide but not yet complete range of serum-antigen proportions has been tested.

THE ANTIGENIC SUBSTANCES OF THE TUBERCLE BACILLUS. L. DIENES.

Dr. Dienes gave a summary of the work of his laboratory on this subject and a short characterization of the chemical and immunologic properties of the antigenic substances of the tubercle bacillus. The antigen demonstrable with the complement fixation and precipitation reaction in vitro in the lipoid extracts of the bacillus can be distinguished from the antigen of a watery extract by the antigenic properties both in vivo and in vitro. The antigen soluble in the lipoid solvents is probably a lipoid composed of a nonlipoidal specific part and of a nonspecific lipoid. The connection of the two parts is probably a chemical one, because both parts suffer a thorough change of their solubility and chemical composition by the separation. It contains no nitrogen. The specific part separated from the lipoids gives complement fixation reaction in the dilution 1:10,000,000, and its potency is increased from 100 to 200 times by the addition of some nonspecific lipoids, for instance the lecithin, beef heart extract. Positive reactions were observed in the dilution 1:400,000,000 of the specific substance activated with lecithin. This mixture of the lecithin and the specific substance contained only 0.01 per cent of the latter. Cholesterin and the lipoid substances of the tubercle bacillus have no activating effect. The precipitation reaction is not activated by the presence of lecithin.

From the observations that in different emulsions of tubercle bacilli and in different watery and sodium hydroxide extract of the bacilli the probable protein content, the antigenic effect in the complement-fixation reaction and the tuberculin effect run fairly parallel, and in the extract together with the precipitation of proteins both specific effects are diminished in a measure corresponding to the precipitation of the proteins, it was concluded that it is probable that both specific effects investigated are the effect of the protein substances. This probability is not lessened by the discovery of a nonprotein precipitable substance in the extracts, because the latter (prepared according to Laidlow and Dudley) gave no complement fixation with our serums, although the serums gave strong precipitation with it; and several serums giving complement fixation in high dilutions with the protein substances gave no precipitation with the nonprotein precipitable substance.

The protein substances are probably the substratum of the complement-fixation reaction (in a watery extract) and of the tuberculin effect. They are very active antigens in vivo. The protein substances determine the specificity of the immune serums in the complement-fixation test. Serums obtained with a bacillary emulsion usually contain less antibodies against the lipoid antigen than against the protein substances. The lipoid antigen separated from the bacterium is only slightly active in vivo. Similar antigens, not distinguishable in the absorption experiment, are present in some acid-fast saprophitic strains. The purified nonprotein precipitable substance is described to be nonantigenic in vivo. A similar antigen was found in the extract of the smegma bacillus.

DISCUSSION

STUART MUDD: The statement that alcohol extracts of the acid-fasts are not specific is not in accord with results at the Phipps Institute. Reactions

with alcoholic extracts and with the oil-miscible surfaces of the intact bacilli of many species have shown serologic specificity.

H. ZINSSER: There seems to be a fundamental difference between the results reported by Dr. Dienes and our own experience. All the work that has been done in our laboratory during the past four years tends to indicate that the substances which are responsible for precipitation and complement fixation with the specific bacterial antibodies are separable from those which cause the tuberculin reaction. This point was not clear in our first work, in which we succeeded only in separating the true anaphylactic reactions from the skin tuberculin effects, but later we published with Mrs. Parker a series of experiments in which it was briefly shown that both precipitation and complement fixation can be obtained with the substance we have spoken of as "residue antigens," the "soluble specific" substance of Avery and Heidelberger, and which has turned out to be carbohydrate in structure. An important feature of such fixations, which might possibly lead to discrepancies, is the fact that in doing complement fixations with these materials the zone phenomenon, namely, the importance of using proportionate amounts of the residue substances and the serums, respectively, plays a prominent rôle. If proper relative amounts of the two reagents are not used, the reactions will be unsatisfactory. Mrs. Parker later showed that this balance is very delicate and follows more or less the rules observed by Dean in his earlier study. Another possible manner of explaining this discrepancy is offered by the different types of antibodies that may be formed by the different parts of the bacterial antigen, such as those published last year by ourselves with Tamyia, which are in keeping with the similar studies of Avery and Heidelberger, namely, that antibodies produced with the whole bacteria react by precipitation and complement fixation with the residue or carbohydrate antigens; those formed in response to injections of dissolved bacteria or bacterial nucleoproteins react only with the protein constituents of the bacterial body in a less specific manner. It is not impossible that it is this type of complement fixation that Dr. Dienes encountered.

However this may be, both our studies on the nature of tuberculin allergy and the chemical studies carried out in our laboratory by Mueller and others have convinced us that the two substances, namely, the specific, complement-fixing and precipitable antigen which is carbohydrate and the probably protein material that is responsible for the skin reactions in tuberculous pigs can be separated; and recent English work has seemed to confirm these results. One of the students in our laboratory, moreover, Abadjief, has repeated the complement-fixation reactions with the residue substance derived from tubercle bacilli since Dienes' first reports appeared, and has fully confirmed the observation that these substances, which do not give skin reactions in tuberculous animals, will fix complement if proper proportions between the reacting substances are maintained. The fact that these non-skin-reacting substances precipitate with antitubercle bacillus serum is almost a routine observation in our laboratory in the evaluation of the biologic activity of the carbohydrate substance. Much of the discussion of Dr. Dienes' results should be made on the basis of chemical observations, and since these are being carried out in our laboratory largely by Dr. Mueller, we will refer this part of the discussion to him.

DR. MUELLER: It has been possible in our laboratory to separate readily the material giving the specific precipitin test and complement-fixation reaction with serum of rabbits immunized by injections of dead tubercle bacilli from that giving the skin test in tuberculous guinea-pigs. The former substance,

when sufficiently purified, both by Laidlaw and Dudley and by us, has proved to be a carbohydrate gum, practically free from nitrogen. The skin reaction, on the other hand, appears always to be associated with proteins, but so far has not been obtained in pure form. The carbohydrate gum, or residue antigen, was found to be active in extremely low concentration as an antigen in the complement-fixation test with immune serum by Dr. Stella Litarczek, and a more thorough comparative study of both fractions was made by Abadjieff, whose paper is now in press.

It may be well to outline a simple experiment by which the separation may be demonstrated, without purification of either fraction. To ordinary old tuberculin, two volumes of alcohol are added, and the precipitate centrifuged down and discarded. Three more volumes of alcohol are added to the supernatant, and the precipitate, after centrifuging, is made up with saline to the volume of the original old tuberculin. The alcoholic supernatant is evaporated on the water bath to a syrup, and made up with saline to the same volume. Both solutions may then be used for the various tests. The two to five volume alcohol precipitate fraction will be found to give strong specific precipitin and complement-fixation tests with immune serum, and a very weak skin reaction. In the alcoholic supernatant fraction the order will be exactly reversed.

I am unable to explain satisfactorily Dr. Dienes' failure to obtain evidence of such a separation. It is not unlikely that the method he has described in his publications, i. e., acidification to the maximum flocculation point, which occurs at about p_H 3, followed by long heating at 100 C., leads to the destruction through hydrolysis of most of the carbohydrate residue. As Heidelberger and Avery have shown, the bacterial protein itself does give a precipitin test in a relatively concentrated solution, and hence probably some complement fixation. It may be that this point will explain some of the discrepancy between Dienes' results and our own.

L. Dienes: A protocol was read according to which the precipitation of a watery extract of the tubercle bacillus at room temperature with the addition of 0.5 per cent acetic acid did not decrease the titer of the extract for the precipitation test, but the titer for the complement fixation was decreased to $\frac{1}{30}$ of the original value. With the serum used in this experiment the two reactions were sharply distinguished. There are differences in the experimental technic used by Zinsser and Mueller and by us which may possibly account for the difference in the results concerning the antigenic properties of the nonprotein precipitable substance for the complement fixation. We used the technic of Laidlow and Dudley for the purification of the substance, which excludes the presence of the protein antigen in the preparation, but may be more injurious to the preparation than the technic of Mueller. In the preparation of the immune serums we bled our animals according to the content of the serum in complement-fixating antibodies, and a number of the serums contained only a trace or no precipitin. But even with serums giving strong precipitation and using a watery extract as antigen no parallelism was found between the results of the complement-fixation test and the precipitation.

Immunologic Studies in Tuberculosis. IV. Concerning the Resistance to Infection of Animals Sensitized with Killed Tubercle Bacilli. S. A. Petroff and F. W. Stewart.

Normal guinea-pigs received intraperitoneal injections on three occasions, at four day intervals, with a suspension of tubercle bacilli of human origin, killed at 100 C. for one hour. Within from ten to twenty days the animals

became hypersensitive and reacted not only intracutaneously to tuberculin, but also to various allergic phenomena, i. e., Koch's intracutaneous phenomenon, the pleural reaction of Paterson and the testicular reaction of Long. This hypersensitive state persisted in a large number of the animals for 400 days or more.

Resistance to infection could also be demonstrated in a large series of guinea-pigs. Ninety-seven sensitized animals and ninety-six controls were studied. The average duration of life of the sensitized animals was 193 days, and that of the controls 147 days.

We believe the fault with all experiments of this nature to be in the selection of the dosage for infection. If we take Calmette's figures that 1 mg. of tubercule bacilli contains 40,000,000 organisms, it is apparent that all our infecting doses (0.001 to 0.004 mg.) were overwhelming, and that each animal received enough organisms to kill at least from 4,000 to 6,000 guinea-pigs. We have demonstrated repeatedly that 10 tubercle bacilli can produce progressive disease in guinea-pigs. It is obvious then that all experiments performed in the past must be repeated but using a small infecting dose. A new method for counting tubercle bacilli has been devised in our laboratory by Dr. F. B. Jennings, Jr., which we expect to prove of great value for counting organisms.

Another difficulty encountered in experiments of this type was death due to intercurrent disease, which occurred mostly in sensitized and not so often in control animals. Over 50 per cent of the animals died of pneumonia, and the cause was found to be the Friedländer bacillus.

The conclusion drawn was that a degree of immunity can be established in guinea-pigs by sensitization with dead tubercle bacilli.

Hypersensitiveness Following the Administration of Placental Extract.

George H. Smith and Luther K. Musselman.

Guinea-pigs sensitized with extracts of human placental tissue reacted to injection of serum from women only and not to injection of serum from men.

A Bacteriologic Study in Cases of Postoperative Thrombosis and Embolism.

E. C. Rosenow.

Partial tension cultures have been made in five cases of postoperative pulmonary embolism secondary to thrombosis of iliac or femoral veins and one case of portal thrombosis. The thrombus and embolus were removed in as sterile a manner as possible and washed repeatedly in large amounts of sodium chloride solution, or the surface was seared with a searing blade. Emulsions in broth or sodium chloride solution made by grinding in a sterile mortar with sand and small pieces of the thrombus were inoculated into tall tubes of melted glucose brain agar, brain broth and other mediums. Similar cultures were made from the blood and from the pipettings from the spleen, liver and kidneys. Necropsy in all of these cases was performed within twelve hours after death. A diplococcus similar to the one obtained twelve years ago in similar cases in Chicago was isolated from the embolus and thrombus in each of the five cases of pulmonary embolism and from the thrombus in the case of portal thrombosis. A staphylococcus was also obtained from emulsions in two cases. The number of colonies of the diplococci was not large, never more than 500 per gram of thrombus. The colonies could be seen growing on the edges of the pieces planted into the soft glucose brain agar. Primary aerobic cultures on blood agar were always sterile, but subcultures grew readily on aerobic blood agar plates. The blood from the heart, liver, spleen and kidneys

was sterile in four cases. The diplococcus was obtained from the blood in one instance only. In one case of sudden death from pulmonary embolism following amputation of the breast for ulcerating carcinoma and in which marked cellulitis with septic fever occurred, a hemolytic streptococcus was isolated from the wound and blood in pure culture and from the pulmonary embolus and iliac thrombus in mixture with the diplococcus. In the case of portal thrombosis associated with peritonitis following gastrectomy for carcinoma of the stomach, *B. coli* and *B. welchii* were found in addition to the diplococcus. Cultures from the blood yielded *B. coli*. The organism isolated from the thrombus was much alike in the different cases. It is a gram-positive diplococcus; its size, shape and grouping resembles the pneumococcus closely, but it is free from a capsule, and the individual cocci are more nearly round. It produces small, dry, non-adherent colonies on horse blood agar plates, which are usually surrounded by a green or brownish green zone of partial hemolysis. The diplococcus is of low general virulence, it does not grow well in citrated blood in vitro, it shortens the coagulation times of the blood markedly and tends to incite thrombosis in animals following intravenous and other injections. It has been demonstrated microscopically in the thrombi produced experimentally and in the thrombus or pulmonary embolus of all but two of twenty-five patients that died of postoperative pulmonary embolism.

Two of the strains fermented inulin and salicin; one of these also fermented mannite; the rest did not ferment these sugars. All fermented glucose, lactose and raffinose.

FURTHER OBSERVATIONS ON THE STREPTOCOCCUS TOXINS AND THEIR ANTITOXINS AND THE STANDARDIZATION OF THERAPEUTIC SERUMS. MARY B. KIRKBRIDE and MARY W. WHEELER.

Toxicity tests on goats indicated no fundamental qualitative or quantitative differences in the toxin of hemolytic streptococci from scarlet fever or from other infections; toxicity tests on human subjects were apparently not as dependable, as the same toxins induced variable reactions in different persons.

As a result of titration tests on goats with eighty serums, including trial bleedings, confirmed with tests of sixteen serums on human subjects, a method for standardizing scarlet fever antistreptococcus serums on goats has been developed. This depends on comparative tests of the test serums with a standard serum against a test dose of a standard toxin, made at the same time, on the same animal, under carefully controlled conditions.

DISCUSSION

W. H. PARK: While no differences are noted in the reaction with goats, the fact that human beings do show variations may indicate that there are real differences in the serum and that man is a better test animal for such differences.

THE PREPARATION AND CLINICAL APPLICATION OF SCARLET FEVER ANTITOXIN. JOHN F. ANDERSON and GEORGE F. LEONARD.

This paper reports the results of the immunization of eighty-four horses for the preparation of streptococcus scarlet fever antitoxin prepared according to the methods described and developed by the Dicks. The horses were immunized chiefly by the injection of either filtered broth cultures of scarlet fever streptococci or by the injection of fresh cultures of scarlet fever streptococci which had been passed through a Sharpless centrifuge. The horses received toxin testing as high as 100,000 skin test doses per cubic centimeter.

Five different strains of scarlet fever streptococci were used in connection with the immunization of the horses. The antitoxin was concentrated by the Banzhof process.

A report was made of 130 severe and moderately severe scarlet fever cases in three institutions in three different states in which the patients were treated with this antitoxin, as compared with the results in eighty-four patients in the same institutions who received no antitoxin. Among the 130 cases, some of which were severe, with marked toxemia, there were no deaths, and only 4.6 per cent developed complications, none of a severe character or requiring surgical intervention. In the eighty-four mild cases without antitoxin, there were no deaths, but in 28.6 per cent there were complications and sequelae of varying degrees of severity. Some of the complications were grave, requiring surgical intervention, and consisted of nephritis of a serious grade, otitis media, mastoiditis and suppurating cervical adenitis.

The following amount of antitoxin was given in the three institutions:

	Dosage		
Hospital	Maximum	Minimum	Average
A	520,000 neutralizing doses	80,000	221,750
B	300,000 neutralizing doses	75,000	137,850
C	600,000 neutralizing doses	200,000	256,800

The results as reported are summarized as follows:

Specific scarlet fever antitoxin may be prepared by the immunization of horses with filtered toxin.

Such antitoxin is specific against scarlet fever occurring in widely separated sections of the United States.

A properly prepared and standardized antitoxin is effective as a prophylactic when used in adequate doses.

When used for passive immunization, it should be given in not less than one half of the average therapeutic dose.

A properly prepared and standardized scarlet fever antitoxin is effective in the treatment of scarlet fever, saving life and reducing the severity and frequency of complications.

DISCUSSION

W. H. PARK: It happens that in our work we have used only a very few horses, but one half of these horses have been on the Dochez method and one half on the so-called Dick method. The most potent horse was on the Dick method, but one almost as good was on the Dochez method, and the fact that we have been using the serum made by both methods with excellent results seems to me to show that either method will give highly potent and useful serum. Apparently, one depends rather more on a suitable horse than on the method. As far as the annoyance for the Dochez method goes, there is little annoyance if you have the Dochez scarlet fever horses in separate stables. There is little trouble from the abscesses. They are small, and in a week or so heal up entirely.

There is another point that I want to discuss, and that is the question as to whether we should inject the serum to prevent scarlet fever in those who have been exposed. I agree with Dr. Anderson that practically every patient will be protected for ten days or two weeks. On the other hand, we have the difficulty that contagion will probably persist longer than that in any institution or family, and the dose will have to be repeated. Unquestionably, a

greater serum reaction is obtained from the present refined serum than from the refined diphtheria antitoxin, and there is a still greater difference if unrefined serum is used. This is probably due to the fact that there has been no time to age the serum. Scarlet fever is not a very contagious disease. In New York City, about one in ten of children exposed in families will develop scarlet fever. I prefer therefore to perform an immediate Dick test, and then if the child or person develops a sore throat or the slightest clinical evidence of scarlet fever, to give a therapeutic dose of the serum. I have had a successful experience in certain institutions and families when we have used this method. So far, in over 100 exposed patients so treated only one case of scarlet fever has developed.

M. B. KIRKBRIDE: At the state laboratory in Albany, a few horses were immunized by both methods, but combining the methods gave the more potent serum.

E. C. ROSENOW: Two children with scarlet fever of mild type apparently, were given antitoxin intramuscularly in the buttock. Six days later, each developed a rash, severe gastro-enteritis and high fever. One child developed a pelvic abscess, possibly from the deep injection reaching some infected retroperitoneal lymph nodes. Dangers of this method of injection are emphasized.

J. EWING: I had a patient, a child with scarlet fever and anemia, possibly of the von Jaksch type, in whom general enlargement of lymph nodes followed injection of scarlet fever antitoxin.

J. F. ANDERSON: I would not advocate scarlet fever antitoxin for preventive purposes, and I believe that a prophylactic dose of antitoxin should be given only if it is demanded. I have never used the Dochez technic, only Zinsser's method, although I am studying the different methods.

STANDARDIZATION OF SCARLET FEVER ANTITOXIN. WILLIAM H. PARK.

Difficulties are encountered in carrying out the Dick method of standardizing scarlet fever antitoxin. The subjects must be human beings who while strongly positive to the Dick test are not sensitive to the horse serum containing the antitoxin to be tested.

Some persons who show the same degree of reaction to the Dick test as others do not respond equally. Unless a great many tests are carried out, it is impossible to test the potency of a serum within fine limits.

As a substitute for human beings, certain breeds of goats have been used by Kirkbride and Wheeler with success. They respond to even smaller amounts of toxin than human beings. Some of them are sensitive to horse serum, and all become so a few days after testing. The great advantage is that we are relieved from testing on human beings. The potency of a serum can be tested within broad limits. The Schultz Charlton blanching phenomenon can be used for testing the potency of a serum as brought out by Blake and Dochez. One cubic centimeter of a 1: 100,000 dilution of a serum that neutralized 50,000 Dick skin test doses of toxin caused definite blanching in suitable cases. This method has its difficulties. It is necessary to have access to scarlet fever cases with suitable rashes that will not receive serum treatment. An evenly distributed erythema on the first or second day of its appearance is the best, and it must remain bright for at least eighteen hours. Even then different rashes give different potency tests. Older rashes are not so good and give lower readings. Unless a great many tests are made, only a fair estimate of potency can be made.

All these methods, however, give tests of sufficient accuracy to be used by us in the treatment of cases. A number of us are now arranging to have a large amount of serum standardized so that the standard serum can be compared with the serum to be tested. This will make for more accurate results.

FACTORS INFLUENCING POTENCY OF SCARLATINAL TOXIN. ANNA W. WILLIAMS.

The toxins reported here were all prepared one year or more ago. We have observed the effect of the different factors mentioned both on the potency immediately after preparation and on the permanency of that potency.

1. Amount of Peptone: Two per cent peptone (Digestive Ferments proteose or Parke Davis) gives a stronger toxin than 1 per cent, but the toxin finally drops to about the same potency as the 1 per cent.

2. Blood: The same thing is true for the addition of blood to the mediums. A stronger toxin is produced when blood is added, but the toxicity of the preparation finally drops to about the same as that of the preparation without blood.

3. Reaction: With a less alkaline reaction (p_H 9.4) the toxin is stronger than with a more alkaline one (p_H 8.2) up to the fifth day; after that up to the tenth day the more alkaline medium gives a stronger toxin.

4. Time of Growth in Incubator: The longer growths—7 to 10 days—have given a more stable toxin.

5. Annual Passage: Strains greatly increased in virulence by mouse passage make a much stronger toxin than the original strains, but the drop in toxicity is greater. However, the final potency of the toxin remains appreciably greater than that of the toxin from the original strains.

6. The drop in potency of these very strong toxins is variably rapid. In about two months, they may drop 50 per cent, in another month a half more; after that the drop is slower. In a year a toxin of 40,000 skin doses to 1 cc. dropped to one of 20,000 skin doses to 1 cc., while a mouse passage strain toxin, 200,000 skin doses to 1 cc., dropped to 30,000 skin doses to 1 cc.

THE EFFECT OF CINCHONICS ON PNEUMOCOCCI. I. THE INFLUENCE OF QUININE ON PROLIFERATION AND AUTOLYSIS OF PNEUMOCOCCI, WITH SPECIAL REFERENCE TO THE EFFECT OF HYDROGEN ION CONCENTRATION. RACHEL ASH and MYER SOLIS-COHEN.

The germicidal action of the quinine salts against pneumococci increases with increase in alkalinity. An increase in effectiveness begins to become evident at the reaction of normal blood (p_H 7.4), but its maximum effect is shown in a reaction more alkaline than this.

An interesting phenomenon becomes evident when the effect of quinine in buffered broths of varying hydrogen ion concentrations is studied. In broths of p_H 6.3 to 6.8, of such acidity that growth of pneumococci normally does not occur, pneumococci are stimulated to growth within a certain zone of quinine dilutions (1:15,000 to 1:50,000, quinine hydrochloride, depending on the p_H). No growth occurs in concentrations of quinine higher or lower than those in this zone.

In a study of the effect of quantity of organisms on the pneumococcal action of quinine, it was noted that on diluting the seed culture a dilution was eventually attained that failed to grow in the control tube of broth but that was stimulated to growth in weak dilutions of quinine.

Especially with optochin, growth of pneumococci in very high dilutions was less favorable than in the control tube; in moderate dilutions, growth was as marked or more marked than in the control tubes; in low dilutions inhibition and death of the organisms again became evident.

In the presence of quinine, autolysis of pneumococci within a period of twenty-four hours is extended to a range of hydrogen ion concentration more alkaline (between p_H 5.5 and 7.6) than that in which dissolutions occurs in the absence of quinine (between p_H 5.5 and 6.8). This phenomenon is pronounced in a concentration of 1:4,000, is still markedly evident in a concentration of 1:20,000, but becomes less evident in a concentration of 1:100,000 and practically nonexistent in a dilution as great as 1:400,000.

There is, furthermore, a tendency, particularly in the alkaline broths, for autolysis to occur at an earlier period in dilutions of quinine than in the broth control tubes.

DISCUSSION

C. W. JUNGEBLUT: Were tests made to determine specificity of fastness and were virulence and cultural and serologic characteristics of the fast strains studied? I would draw attention also to specific hypersensitiveness in bacteria as described by Schnabel in 1922.

MYER SOLIS-COHEN: The points about which questions were asked are reserved for study later.

CONTRASTED BEHAVIOR OF PNEUMOCOCCI TOWARD QUININE AND OPTOCHIN IN RELATION TO DRUG-FASTNESS. RACHEL ASH and MYER SOLIS-COHEN.

Resistance of pneumococci to optochin may be developed quickly. Within an experimental period of from twenty-four to forty-eight hours there is acquired an insusceptibility to concentrations ten and more times as great as that in which growth of the untreated culture is inhibited. In our experiments, resistance developed whether the organisms were continuously or intermittently exposed to optochin.

Various experimental methods were tried to determine whether pneumococci can become insusceptible to the germicidal action of quinine on prolonged exposure to a salt of this alkaloid. The experimental periods ranged from ten to thirteen days. In one series of experiments, 10 per cent of the cultures eventually grew in the highest dilution in which the control culture failed to grow. In no other series could even this extent of resistance be demonstrated. Against quinine, therefore, pneumococci do not show a similar tendency to the development of resistance.

A SPECIFIC PNEUMOCOCCUS TOXIN. J. G. OLSON.

Filtrates from broth cultures of the pneumococcus, twenty-four hours old, have been the subject of study and have been found to exhibit certain specific toxic characteristics.

Such filtrates give rise to cutaneous reactions in man (Proc. Soc. Exper. Biol. & Med. **18**:294, 1926) and in suitable animals, e. g., rabbits.

Injected into mice, intraperitoneally, they exert a toxic action manifested grossly especially in the lungs, and histologically in the lungs, liver and spleen. Our pathologic studies are being made by Dr. E. Vernon Hahn of the department of pathology, Indiana University Medical School. The histologic changes in the lung consist of interstitial hemorrhage, with pressure atelectasis and varying amounts of interalveolar extravasation. Macrophages, laden with blood pigment are common, and a polymorphonuclear reaction of varying degree is

commonly seen. We have seen striking examples of perivascular lymphoid hyperplasia. Catarrhal reaction with edema, vacuolization and degeneration of the alveolar and bronchiolar epithelium are present.

The liver shows areas of central lymphoid hyperplasia, with fatty degeneration throughout. Increased numbers of Kupffer cells are seen, and there is a definite nuclear pyknosis.

Filtrates capable of exerting such effects have been rendered innocuous by boiling.

Mice have been actively immunized by the serial injection of filtrates against several thousand fatal doses of pneumococci.

The toxin apparently is not type specific.

Normal serums from horses, sheep, rabbits and chickens have been found to possess very little power to neutralize the toxicity of our pneumococcus filtrates. The same is true of ordinary antipneumococcus serums or antibody solution and such immune serums as scarlet fever antitoxin, dipthheria antitoxin or antistreptococcus serum.

A Specific Pneumococcus Antitoxin. G. H. A. Clowes, W. A. Jamieson and J. G. Olson.

We have been working on the production of specific pneumococcus antitoxins for about two years, and have made use of the Dochez and Larson procedures as well as the injection of the specific pneumococcus toxin itself.

Extensive experiments were tried principally on rabbits and sheep, using Larson's procedure, which consists in the injection of whole culture, appropriately attenuated by means of a highly purified castor oil soap. Recently we have obtained somewhat better results from the subcutaneous injection of increasing doses of sterile pneumococcus toxin.

Various methods of determining the potency of our antitoxins have been used: (1) A series of dilutions of antitoxin are prepared and incubated together with a fixed amount of toxin, such that 0.1 cc. contains 25 rabbit skin test doses. Thus the quantity of serum required to neutralize 25 skin test doses is determined. (2) A series of dilutions are prepared and incubated together with a fixed amount of toxin capable of producing a characteristic pathologic condition in the lungs of mice. In general, about 5,000 rabbit skin test doses are required. The animals in question, together with controls, are killed with chloroform vapor at the end of twenty-four hours. The quantity of antitoxin necessary to protect the mice is determined by immediate necropsy of the animals. (3) The toxin when injected intravenously into dogs produces a characteristic respiratory depression which may be inhibited by previously admixing the toxin with the antitoxin.

Our work indicates that neither the pneumococcus toxins nor the antitoxins we have obtained are type specific. This has been determined by cross titration methods.

George B. Walden and Jasper P. Scott, working with one of us (Clowes), have succeeded in purifying the pneumococcus antitoxin to the extent of removing over 99 per cent of the associated serum proteins, without appreciable loss of antitoxin as measured by the means described. Such concentrated antitoxins are, in their purest form, water white, limpid, nonviscous solutions, capable of being boiled for half an hour without being destroyed.

A chemical investigation of the nature of the purified antitoxins is now being made in the Lilly Research Laboratories.

Clinical experimentation with pneumococcus antitoxin in cases of lobar pneumonia seems to justify further clinical trial on a larger scale.

DISCUSSION

F. P. GAY: Was any method used for concentrating the pneumococcus toxin?

J. F. ANDERSON: Several years ago I immunized several horses by subcutaneous injections of pneumococci and obtained a serum which, however, was not successful clinically, and further study of it was abandoned.

G. H. A. CLOWES: There can be no doubt that we are dealing with a toxin and antitoxin. The mouse protection is definite. It takes a long time for toxin and antitoxin to combine. One definite case of lobar pneumonia was apparently much benefited by pneumococcus antitoxin. There are other factors than toxemia which are responsible for the clinical picture, such as septicemia and the autolysis of the pneumonic exudate. The antitoxin is concentrated by fractionation with sodium chloride by an intricate chemical method which is still being studied and will be reported on later.

IMMUNIZATION WITH TOXINS DETOXIFIED WITH SODIUM RICINOLEATE. W. P. LARSON.

As most toxins are detoxified instantly when appropriately mixed with sodium ricinoleate, their antigenic properties remaining unimpaired, experiments have been made on immunizing both animals and human beings against diphtheria, scarlet fever and other toxins. Diphtheria toxin-soap has been found equal to, and in some respects superior to, toxin-antitoxin as an immunizing agent.

Sodium ricinoleate is an effective agent in detoxifying scarlet fever streptococcic toxins, and such soap toxin mixtures give a rapid immunity without causing objectionable reactions. The sodium ricinoleate method of detoxication makes it possible to give sufficient toxin in a single injection to cause positive skin tests to become negative within a few days.

DISCUSSION

W. H. PARK: Whether we should change the preventive inoculations from straight toxin in scarlet fever to these more or less detoxicated toxoids is an important question. If we use the toxoid in diphtheria, we have a much larger amount of the original toxin present than when toxin-antitoxin is used. Because of this in the older children and especially in adults we get a more marked reaction, while in the children of preschool age and babies, we will have, according to the age, less and less reaction with the toxoids and rather more with the toxin-antitoxin. So far as sensitization goes, there is no question that you do get in some a slight sensitization from the serum in toxin-antitoxin which may last for several years. I have never seen any appreciable harm from this, but I do think it is of some importance, and it is well to avoid it if possible. It is then simply a question as to whether this detoxicated toxin by sodium ricinoleate or formalin is as good an immunizing agent as toxin-antitoxin. In immunizing against scarlet fever, there is no question of sensitization, as no serum is used. In my experience, the Larson product has not been as satisfactory as the straight toxin. The children, when tested after three inoculations, did not show as much immunity as those who had received injections of unaltered toxin, so that I think it is still to be shown in scarlet fever that there is any advantage of toxoids over the toxin. In diphtheria I think a toxoid should be used when we have decided on the best product. Whether it should be used for children of all ages, or perhaps only for the younger ones, can be decided later.

G. H. A. Clowes: The main features of Larson's method is to lower surface tension at a nearly neutral point. It is an important discovery.

W. P. Larson: The titer of toxin used was 3,000 skin test doses, the equivalent of 5,000 by the Dick standard. There is always some free toxin in the treated substance, and this determines the size of the dose.

The Effect of Intravenous Injections of India Ink in the Immunized Animal. C. W. Jungeblut and J. A. Berlot.

Massive doses of India ink injected intravenously into guinea-pigs before immunization with toxin-antitoxin mixture caused a delay in the appearance of diphtheria antitoxin for about one week. Intravenous injections of India ink into guinea-pigs were followed by a transitory drop of the complement titer. Reduction tests (methylene blue and nitro-anthraquinone) showed the respiration of the cells of the liver and spleen of the same animals to be markedly impaired for the first day. India ink injected intravenously in large doses into guinea-pigs before active sensitization caused a more or less marked decrease in sensitiveness to the reinjection of the antigen, while, when injected before passive sensitization, it did not interfere with the occurrence of anaphylactic shock. The precipitin titer of blocked sensitized rabbits was somewhat lower than that of controls. The titer of anaphylactic antibodies differed slightly only in one case.

DISCUSSION

F. P. Gay: The last chart shows clearly that a small amount of India ink will stimulate and a larger dose depress the formation of antibodies.

The Histology of Local Streptococcus Immunity. F. P. Gay and R. W. Linton.

The authors described first the histologic changes that take place in the pleura of rabbits as the result of the injection of sterile aleuronat or gum arabic broth mixtures. These changes are earlier and more marked in the parietal pleura and diaphragm, through which drainage of the pleural cavity takes place, than in the visceral (lung) covering. The changes are similar with the two substances employed, and, owing to the delicacy of the tissue involved, show remarkable differences from normal in the nature of an acute inflammation followed by a more chronic condition in the nature of granulation tissue. Infiltration with polymorphonuclear cells on the first day is replaced by an intensified thickening due to mononuclear cells by the third day. By vital staining with trypan blue, a preponderating number of these mononuclear cells is shown to be true clasmatocytes or tissue macrophages.

The cytology of the pleural exudate is a reflection of the tissue changes here emphasized. There is a definite relation between the cell picture and presence or absence of an increased resistance to infection with a strain of *Streptococcus pyogenes* that produces in minute doses a fatal pleurisy. The correlation indicates that the clasmatocytes are responsible for protection. This correlation is further emphasized by the tissue changes now described. An acute inflammatory pleura is invaded and destroyed by virulent streptococci injected into the pleural cavity, whereas the same organisms disappear rapidly from the pleural cavity of animals with granulating and thickened pleural walls, and are found enveloped within clasmatocytes in a relatively undisturbed tissue. Phagocytosis of streptococci both in the exudate and tissues is carried on almost exclusively by mononuclear cells.

The pleural wall may be thickened still further by repeating the injection of the nonspecific substances or by injecting living streptococci. The degree of protection would seem roughly commensurate with the depth of granulation tissue that has been produced. It is not possible yet to say whether specific immunity produced by the streptococcus differs from increased resistance produced by nonspecific and sterile irritating agents in possessing some specific factor; in other words, whether all grades of local streptococcus protection are dependent simply on the number of clasmatocytes present.

Preliminary experiments show that when one pleural cavity is treated sufficiently, the other cavity, although showing no histologic change in the pleural wall at the time of infection, is nevertheless protected. This protection is accompanied by mobilization of clasmatocytes in the pleural wall in an unusual fashion; there is further indication that the wall of the treated cavity is coincidently stripped of its cells.

DISCUSSION

STUART MUDD: Is there any explanation of the rapid disappearance of the bacteria from the pleural exudate and their appearance in the deeper tissues?

H. G. WELLS: Were any studies made using pleura and pericardium?

F. P. GAY: There is a local destruction of bacteria, but in fifteen minutes 70 per cent left the pleural cavity and entered the deeper tissues. Pericardium was not used. Peritoneum and pleura give inconstant results.

THE WANING SKIN SENSITIVENESS TO TUBERCULIN AND ITS RELATION TO IMMUNITY. H. S. WILLIS.

The most acceptable view of immunity to tuberculosis is that this phenomenon is closely related to hypersensitiveness to tuberculin. We know that hypersensitiveness as shown by the tuberculin reaction in human beings may fluctuate considerably during normal life, becoming very slight or completely absent at times, and developing again at other times. The question of whether immunity to tuberculosis fluctuates in this manner is an engaging one, the answer to which has been sought by the following experiment:

The plan of the experiment was to study tuberculin sensitiveness of the skin of guinea-pigs for a relatively long time after infection and to compare the state of allergy as shown by skin reactivity with the degree of immunity to reinfection. To this end, guinea-pigs were first inoculated with a strain of tubercle bacillus of low virulence (RI) and at trimonthly intervals, beginning one year after infection, a certain number of them were given intracutaneous tests with tuberculin and were, a few days later, inoculated subcutaneously with an emulsion of virulent tubercle bacilli, as were also normal animals.

Normally, the reaction to tuberculin injected into the skin of hypersensitive guinea-pigs is an inflammation, characterized by redness, induration and frequently hemorrhage and necrosis, the height being reached within from twenty-four to forty-eight hours of the injection. The animals in this experiment that were tested with tuberculin one year after the initial, sensitizing inoculation (RI) were found in general to give vigorous reactions. Animals allowed to go eighteen months before a test was made were also found to react but with less vigor. At twenty-one months, the reaction in those tested was still less marked, and usually by twenty-four months no reaction could be elicited with the ordinary doses of tuberculin. Some of the latter animals, however, gave reactions with larger doses of tuberculin.

After each group of animals were tested with tuberculin, they were inoculated with virulent tubercle bacilli (H37). Those receiving the second inoculation, two years after the initial infection, although they had lost their skin sensitiveness, still had a high degree of immunity — as high as had those reinfected at twelve, fifteen, eighteen or twenty-one months after the sensitizing infection, or as had animals reinfected only two or three months after initial infection.

It was interesting to note that although the skin sensitiveness of the animals two years after the initial infection was in abeyance and could not be elicited with the dose of tuberculin ordinarily used, this sensitiveness was quickly restored after reinfection, for the animals four or five days after reinfection exhibited marked reactions to tuberculin.

The question arises as to whether immunity and hypersensitiveness actually coexist *at all times* and whether fluctuation in hypersensitiveness necessarily indicates fluctuation in immunity. It appears that the degree of immunity of infected animals does not decline quantitatively in proportion to the decline of allergy *as we have been accustomed to test these phenomena.* But the failure to give skin reactions is perhaps not to be considered as absolute proof of the complete absence of hypersensitiveness. Is the immune state one of delicate balance which, though not always demonstrable to test, may be present and may very quickly be raised to a high degree? There may be an immunity of minimal stationary degree which is present as long as infection exists or as long as any hypersensitiveness exists, even in slightest degree.

DISCUSSION

L. A. PETROFF: I was very much interested in Dr. Willis' paper. We have been carrying on the same type of experiment for the last four or five years, using, however, dead tubercle bacilli for our sensitization and not the strain of culture used by Dr. Willis, which is R_1, a culture of low virulence. We have found that skin hypersensitiveness produced in guinea-pigs with dead tubercle bacilli is not of the transitory type. A fairly good hypersensitiveness lasting for more than a year can be set up with dead organisms in a normal animal.

Another thing that interested me considerably in Dr. Willis' paper was the relationship noticed between skin hypersensitiveness and immunity in his animals. As I understand from what he tells us, guinea-pigs inoculated with R_1 organisms become skin hypersensitive, which state may last a year or two, after which the animals become skin negative, and at this stage, although not hypersensitive, a degree of resistance could be demonstrated.

Our experience has been somewhat similar to that of Dr. Willis. In a large series of experiments we have noticed that animals treated with dead tubercle and having lost their hypersensitive state still possess some degree of resistance.

I am inclined to believe that we may be wrong in saying skin hypersensitiveness means resistance and that in all probability it has nothing to do with the basic mechanism of immunity.

R. W. MELLON: What was the relation of the time of development of the immunity process to that of the development of skin hypersensitiveness?

L. DIENES: The testing of the cattle in the recent experiments of Calmette has shown similar results. As the test indicates that only a certain grade of hypersensitiveness and the biologic mechanism of the test is not well understood, caution is necessary when drawing any conclusion from it.

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RUTH TUNNICLIFF, M.D., *President, in the Chair*

ORIGIN OF GLYCOGEN IN TUBERCLES. MAX PINNER.

Glycogen appears in tubercles when leukocytes immigrate. It is found in leukocytes, epithelioid cells and in giant cells, in the two latter types whenever they engulf leukocytes. The occasional droplets of glycogen in these cells seem to be the remains of digested leukocytes. The possibility must be considered that small amounts of glycogen may be derived from digested tubercle bacilli. That epithelioid cells actively envelop and digest leukocytes shows that they are not functionally degenerated and devitalized cells.

DISTRIBUTION OF CERTAIN ANTIGENS IN THE BODY. ETHEL B. PERRY and L. HEKTOEN.

Precipitin tests of the organ extracts and various fluids of rabbits after intravenous injections of human hemoglobin and beef lens were made with antiserums for these antigens. No essential differences in their distribution appeared. In pure solutions they both disappeared from the blood and from the organs in about twenty-four hours, but after injections of whole citrated blood, hemoglobin was detected as late as seventy-two hours in the serum and occasionally also in the liver and bile.

Within one-half hour the antigens appeared in the bile, urine, intestinal mucosa and contents, and in different degrees in practically all tissues, revealing not only a general distribution, but also the excretion of a certain portion of antigen unchanged.

The highest concentrations in the organs were in the kidney, bone marrow and omentum; the liver and lymph nodes came next, and the spleen was usually negative after the first few hours.

The relations between the liver and bile were less regular than between the kidney and urine, probably because only a single test of bile could be made while all of the urine could be collected. The antigen content of the fluids and extracts, in general, paralleled that of the serum, but in lower concentrations, and all titers decreased steadily without indication of progressive accumulation or of prolonged retention in any organ.

These results differ from those described by others for cellular antigens only in the shifting of the site of greatest content from the spleen and liver, to the kidney, marrow and omentum. The omentum, known to be rich in clasmatocytes, has been omitted from many studies of antigen distribution.

STREPTOCOCCUS ERYSIPELATIS TOXIN AND ANTITOXIN. HARRY A. SINGER and BERTHA KAPLAN.

In attempts to produce local blanching of erysipelas lesions by erysipelas convalescent serum, it was observed that although complete disappearance of the inflammation did not occur at the site of inoculation of the serum, a beneficial effect did result. This neutralizing effect is attributed to bodies in the convalescent serum.

In order to study these immune bodies further, a preliminary study was made of skin reactions in patients with erysipelas, using a sterile toxic filtrate of a culture of *Streptococcus erysipelatis*. It was noted in a series of erysipelas

cases that as the disease subsided the skin reactions using the same amounts and concentrations of toxic filtrate became less and less marked or entirely negative.

Since the filtrate employed resembled in its properties the Dick scarlet fever toxin in regard to the skin reactions provoked and in its resistance to heat, it seemed that it might contain a true toxin. If this were the case, the filtrate (toxin) should, when injected into animals or man, be capable of producing within the body a neutralizing substance (antitoxin).

Two highly susceptible persons were immunized by injections of increasing doses of erysipelas sterile filtrate (toxin), the immunity being indicated by decreasing sensitiveness to increasing skin doses. Serum collected before the inoculations were begun failed to neutralize erysipelas or scarlet fever toxin in dilutions of 1:100, whereas following the immunization, the serum from the same persons exerted a powerful neutralizing effect on not only diluted but also undiluted toxin of both the erysipelas and scarlet fever types.

Further neutralization studies showed a greater protective value of the artificially produced immune erysipelas serum (antitoxin) as compared with that of the convalescent erysipelas serum. Blanching, using now the antitoxin in place of the convalescent serum, occurred in 50 per cent of the cases tested, indicating again a relatively higher potency of the antitoxin. From a study of the literature, especially of the work of Rivers and of Birkhaug, the impression was gained that the serum obtained by inoculation of toxin alone compared favorably in its protective qualities with the anti-erysipelas serum produced by inoculation of the organisms.

Cross neutralization tests using various combinations of erysipelas and scarlet fever toxin and antitoxin led to the conclusion that absolute specificity was lacking. However, it should be borne in mind that throughout the work, in order to obtain comparative results in neutralization experiments, but two strains of *Streptococcus erysipelatis* were used and but one strain of scarlet fever streptococcus. It is conceivable that the strains employed belong to the small group of nonspecific hemolytic streptococci described by other workers in their classifications on the basis of various biologic tests.

CONCLUSIONS

The sterile toxic filtrate of a broth culture of *Streptococcus erysipelatis* possesses the properties of a true toxin.

The erysipelas toxin is capable when injected into man of provoking the formation of a neutralizing substance (antitoxin).

The artificially produced immune serum (antitoxin) has a greater potency than convalescent erysipelas serum.

The antitoxin produced by injections of toxin alone seems to compare in its protective qualities with anti-erysipelas serum obtained by others from animals by the injection of organisms.

The hemolytic streptococci of erysipelas and scarlet fever are not biologically absolutely specific.

SYPHILIS OF THE LUNG. GEORGE J. RUKSTINAT.

This article will be published in full in the ARCHIVES OF PATHOLOGY AND LABORATORY MEDICINE.

Book Reviews

THE NEMATODE PARASITES OF VERTEBRATES. By WARRINGTON YORKE, M.D., Professor Parasitology, University of Liverpool and Liverpool School of Tropical Medicine; and P. A. MAPLESTONE, M.D., D.S.O., with a foreword by C. W. STILES, Professor of Zoology United States Public Health Service. Price, $9. Pp. 536, 307 illustrations. Philadelphia: P. Blakiston's Son & Company.

This book is not a mere compilation of genera and species but is a critical study, with considerable original work, of the parasitic nematodes of vertebrates from the point of view of a systematic zoologist. The object that the authors had in mind in writing the book was to simplify the process of identifying nematode parasites. Owing to the increase in the number of genera and species of parasitic nematodes during the past few years, and the changing conceptions as to their zoological relationships, the problem of identifying and of allocating to their respective groups specimens of nematodes had become an almost hopeless task to most workers who were not primarily concerned with this field of investigation. Even among parasitologists only a limited number of workers have been able to keep abreast of the progress in the study of systematic nematology, by virtue of their highly specialized training and interests and their proximity to leading libraries and museums. Yorke and Maplestone have collected and, in a large number of cases, have restudied the pertinent available information on the subject and have condensed it in a single volume, thus placing at the disposal of parasitologists and other workers a compact library on nematode parasites heretofore available only in about half a dozen library centers.

The book deals with the various systematic groups of nematodes as far as genera, and contains dichotomous keys for determining the systematic status of the parasites involved. There are no descriptions of species, the latter being listed under each genus together with their host or hosts. The generic descriptions are based in most instances on the type species and are illustrated with 307 excellent sketches, many of which are original. In view of the large number of species, genera, and higher groups that are dealt with, the book is remarkably free from nomenclatural and other errors, and is without question the most authentic general work of reference on parasitic nematodes.

Those whose interests in nematodes are limited to forms occurring in man, will find in Yorke and Maplestone's book concise generic descriptions and original illustrations of such species as *Strongyloides stercoralis, Trichinella spiralis, Trichuris trichiura, Ascaris lumbricoides, Ancylostoma duodenale, Necator americanus, Enterobius vermicularis,* as well as of other species occurring in man.

The value of the book as a work of reference is greatly enhanced by the indexes to generic and specific names which are followed by the names of the authors responsible for them, in accordance with the usages in zoological nomenclature, and by an author's bibliographic index containing about 700 references.

Beyond the technical descriptions of nematode parasites and a discussion of their zoological affinities, the book contains no information concerning the

parasites involved. Its scope is limited strictly to that of a manual of determinative nematology, and as such it will prove indispensible to all workers who have occasion to identify parasitic nematodes.

THE ASPERGILLI. By CHARLES THOM and MARGARET B. CHURCH of the Microbiological Laboratory, Bureau of Chemistry, United States Department of Agriculture. Price, $5. Pp. 272. Baltimore: The Williams and Wilkins Company, 1926.

When Dr. Thom in 1904 began to investigate the part played by molds in the field of food handling, he at once encountered species of *Aspergillus* and met with embarrassment in their identification from available descriptions. For more than twenty years he has been a student of *Aspergillus*, and finally has accumulated about 350 strains, which furnish a basis for the present publication. Being a world authority on this subject, perfectly familiar with the organisms and with the literature relating to them, he and Miss Church have produced such a complete reference work on *Aspergillus* as has not been undertaken previously. Part I, about half of the book, is concerned with a general discussion. Part II is devoted to the nomenclature of *Aspergillus*. There is a synoptical key to all the species of *Aspergillus*, a list of accepted species, and an extensive collection of references. It is safe to predict that for many years this book will be a favorite one for reference by botanist, bacteriologist and students of disease in animals and plants, all of whom will be grateful to the authors for placing the results of their exhaustive research at their disposal in such attractive form.

INSECTS AND DISEASE OF MAN. By CARROLL FOX, M.D., Surgeon, U. S. Public Health Service. Price, $4.00. Pp. 349, with 92 illustrations. Philadelphia: P. Blakiston's Son & Company.

This volume contains a good description of the Arthropods that carry infections, principally those of man. It is enriched with a considerable number of good illustrations, principally diagrammatic, which facilitate the identification of the species described in the text. The author has elected to discuss and classify the insects in the earlier chapters, reserving the last fourteen chapters for the consideration of the diseases transmitted through these insects, together with the methods of prevention. A chapter (22) on rodents is injected rather abruptly between the section on insects and the section on human diseases, a position of debatable value in view of the discussion of rat extermination in chapter 32. The table of contents reflects some looseness in arrangement leading to loss in clarity and repetition. This might be avoided readily in another edition.

The book should be useful to health officers and those interested in insect borne disease.